

ほん ゆう めん だ じゃ ほう
朋友们, 大家好!

うお じいお しあん ちあん ずうあん りあん
我叫山田壮亮。



山田 壮亮

YAMADA Sohsuke, M.D., Ph.D.

Professor and Chair

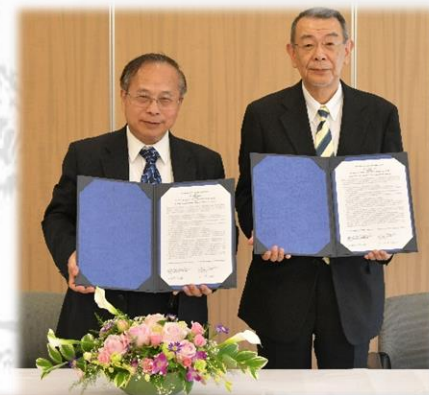
Department of Pathology and Laboratory Medicine

Kanazawa Medical University

May 15th, 2018.

Through our activities

of HOKUSHIN cancer professional training plan.



台日友好 金澤醫科大學組團至高醫暨小港醫院交流

大成報 / 2018.07.25 16:52



The Association of Peroxiredoxin 4 with the Initiation and Progression of Hepatocellular Carcinoma

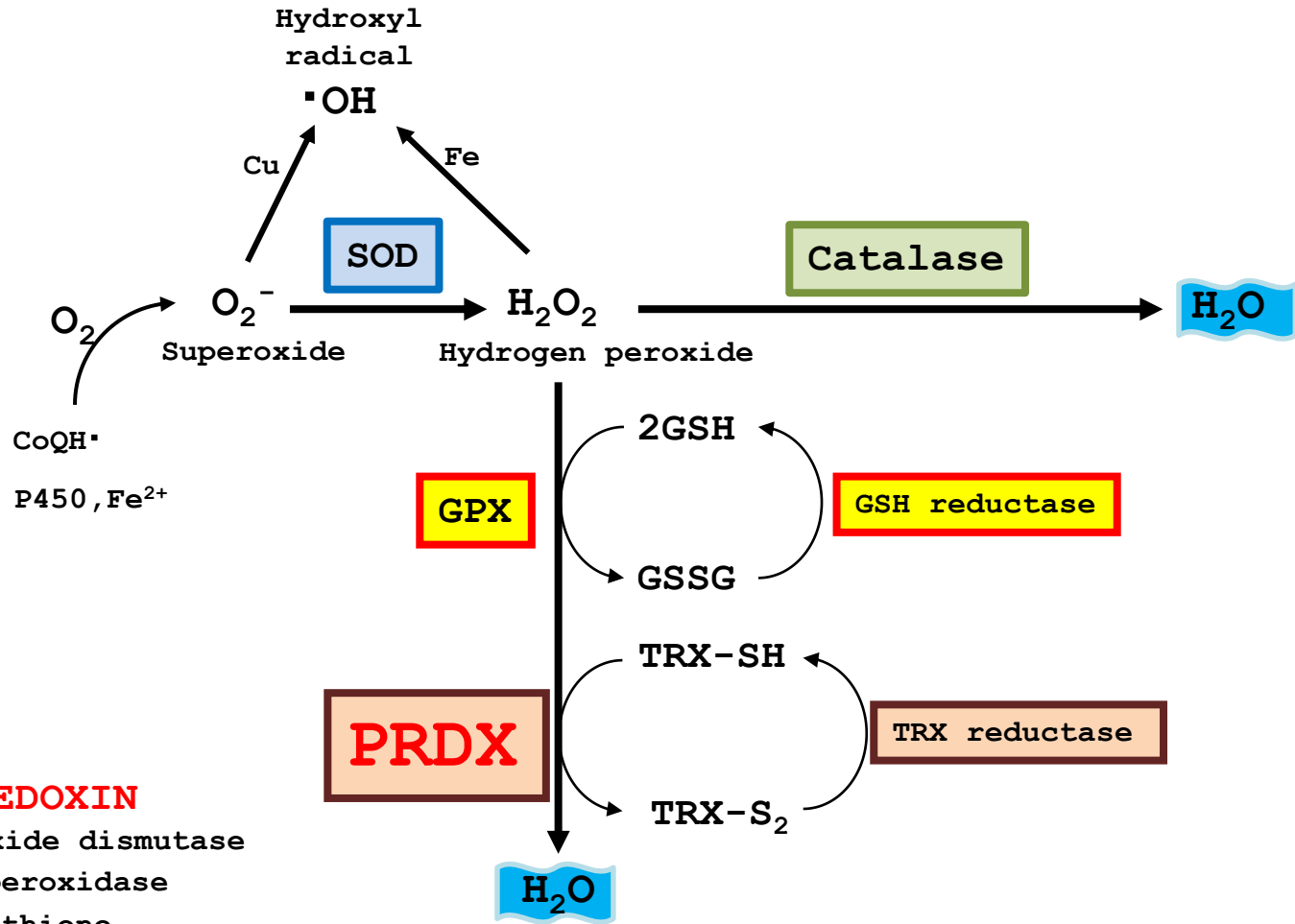


Sohsuke Yamada

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Pathway of the detoxification of ROS



PRDX: PEROXIREDOXIN

SOD: Cu,Zn-superoxide dismutase

GPX: Glutathione peroxidase

GSH: Reduced glutathione

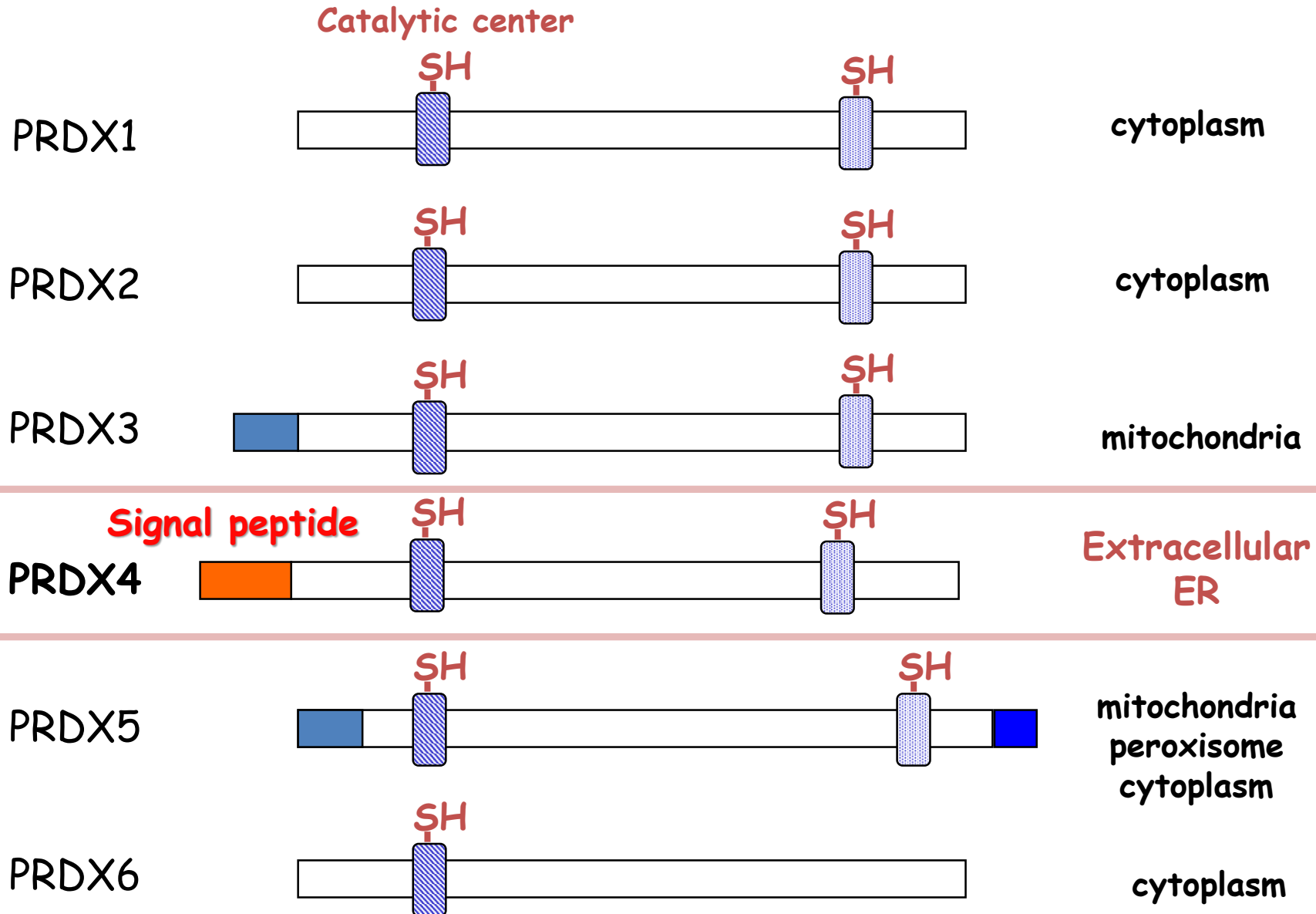
GSSG: Oxidized glutathione

TRX: Thioredoxin

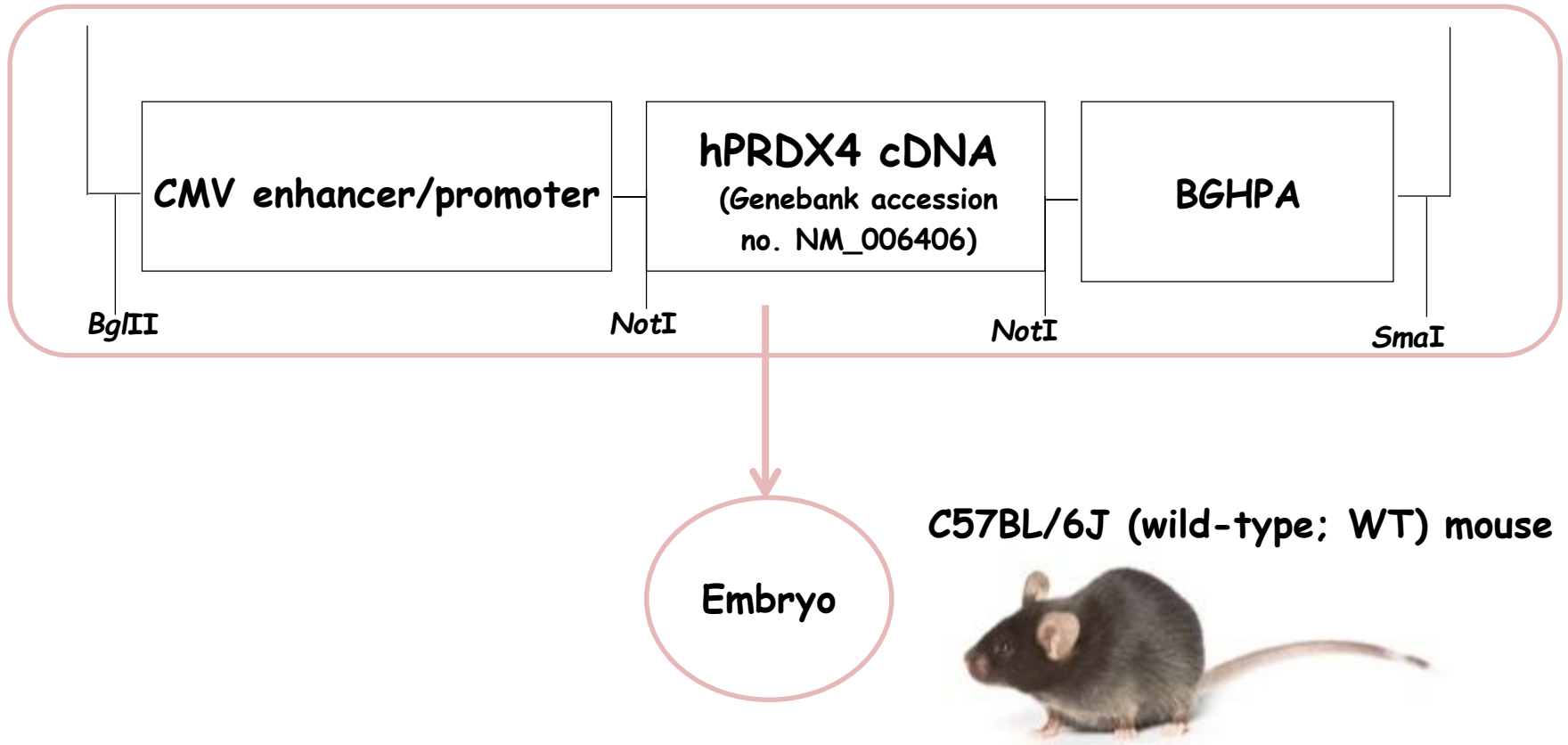
CoQ: Coenzyme Q

P450: Cytochrome P450

Schema of mammalian PRDX family



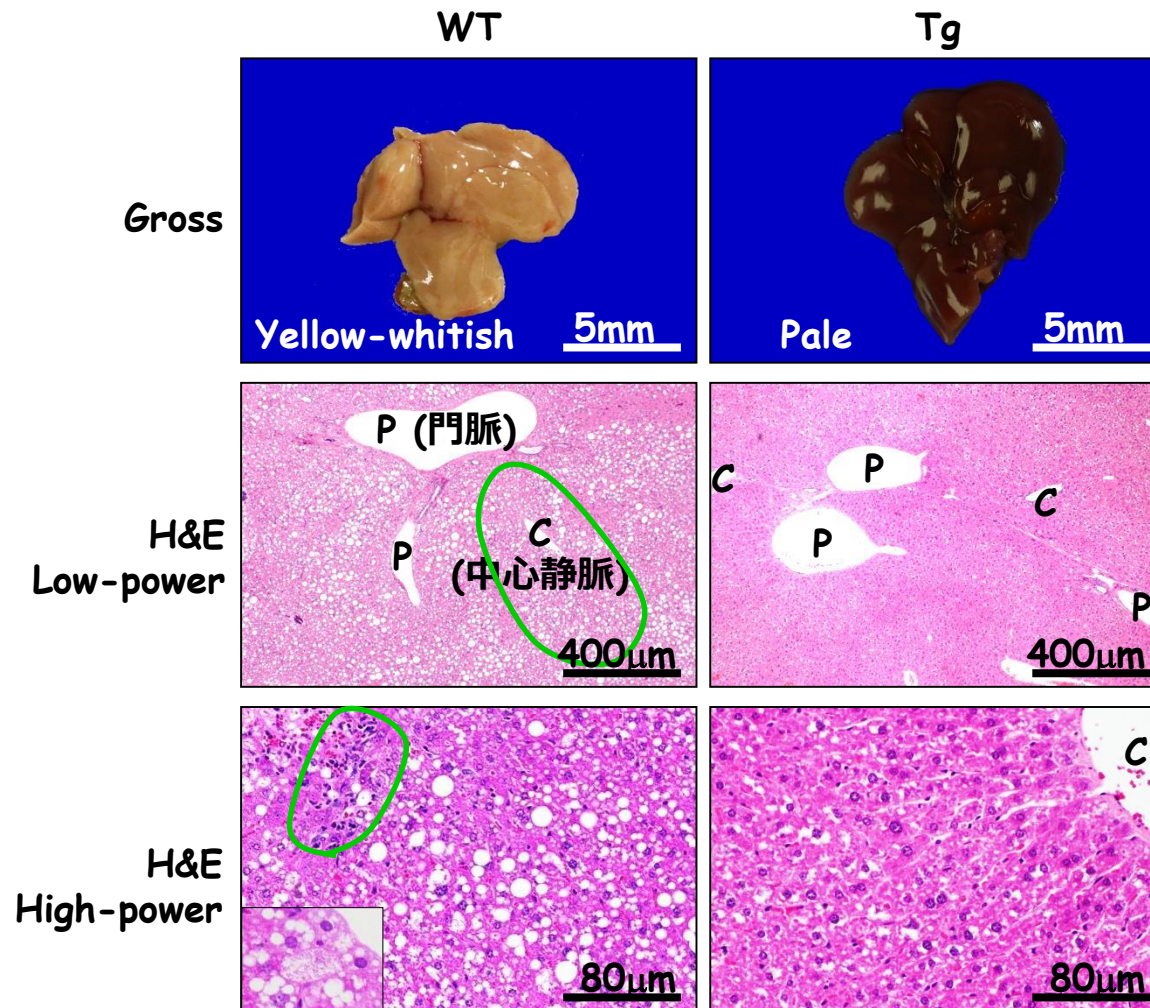
Human PRDX4 (hPRDX4) transgenic mice



The entire nucleic acid sequence was microinjected into the male pronuclei of one-cell C57BL/6 female mouse embryos.

PRDX4 protects against NAFLD

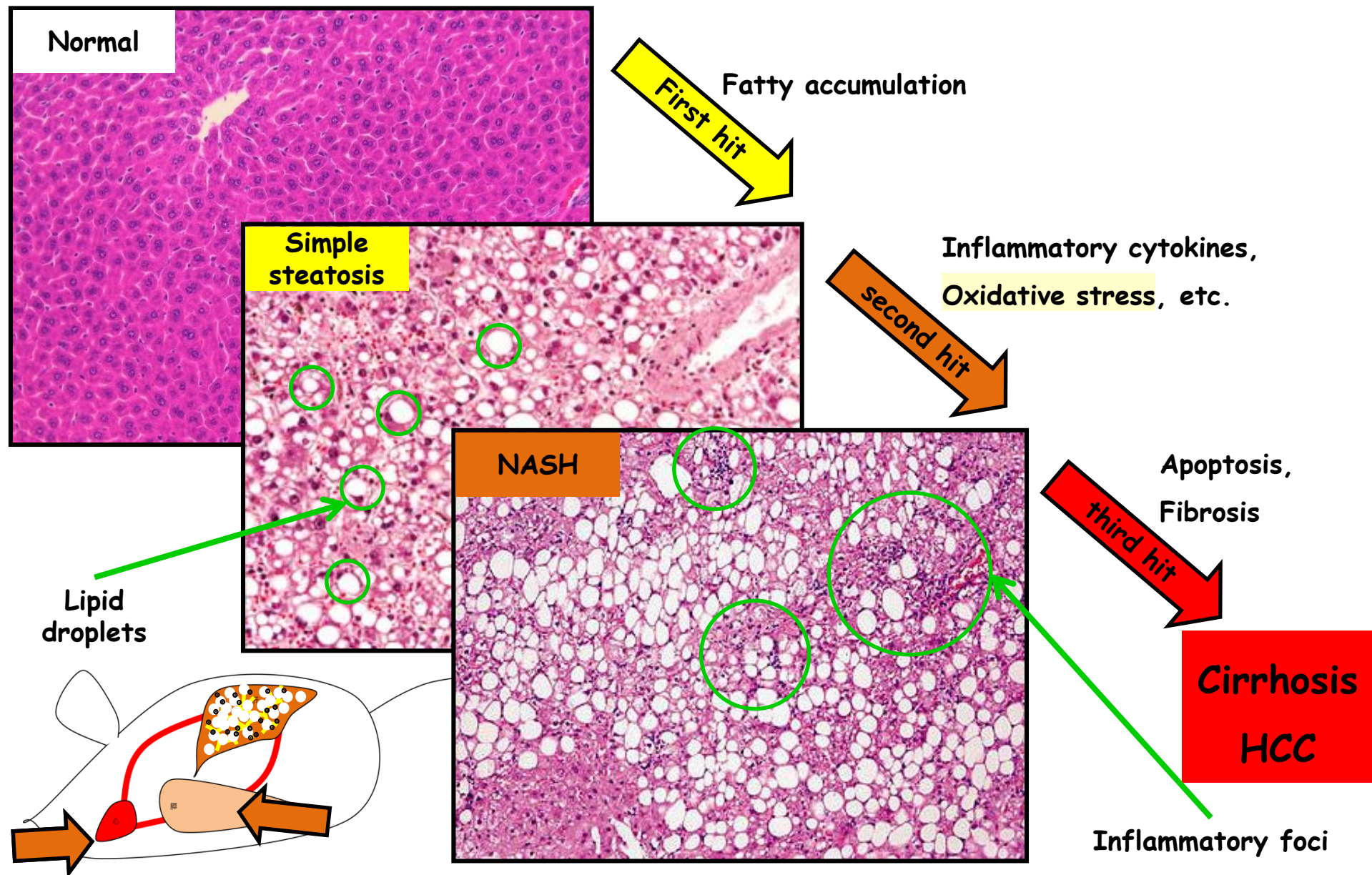
HFrD+STZ model



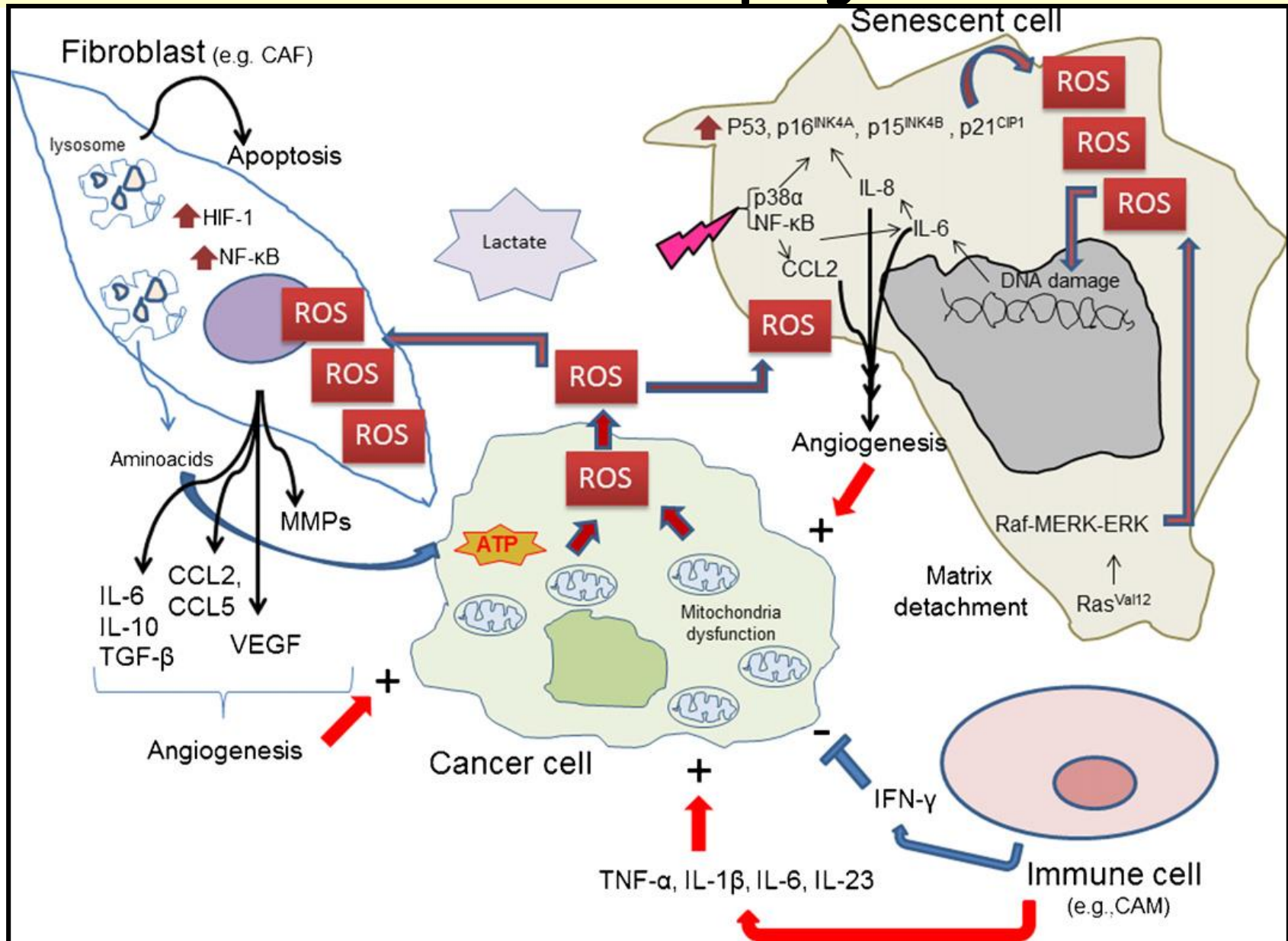
The livers from Tg mice contained no or very few lipid droplets in hepatocytes, and no inflammatory foci.

NASH progression was significantly suppressed in Tg liver.

Two- to Multiple-hits theory in NASH



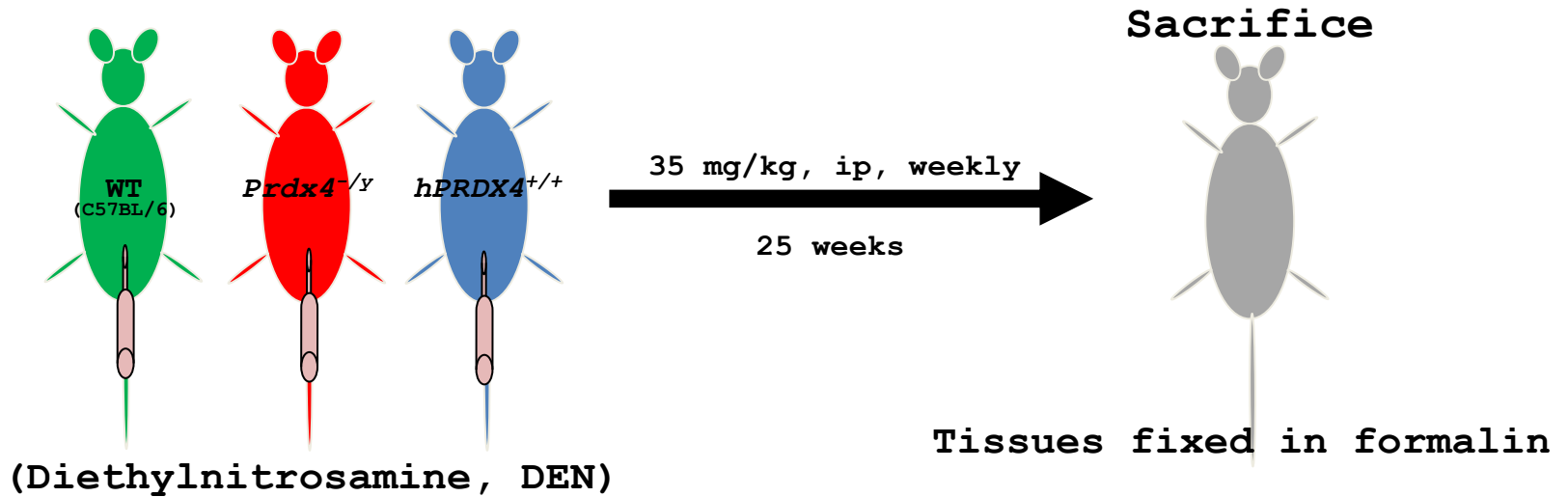
The roles in signal regulation by ROS on HCC initiation/progression





Method ①

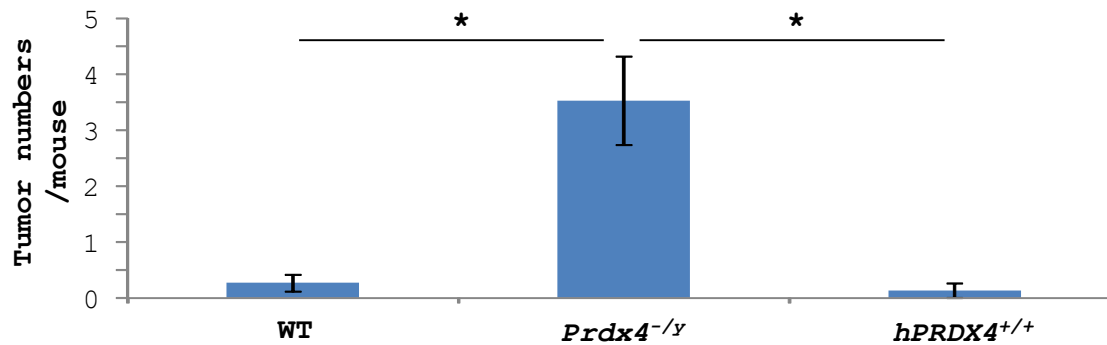
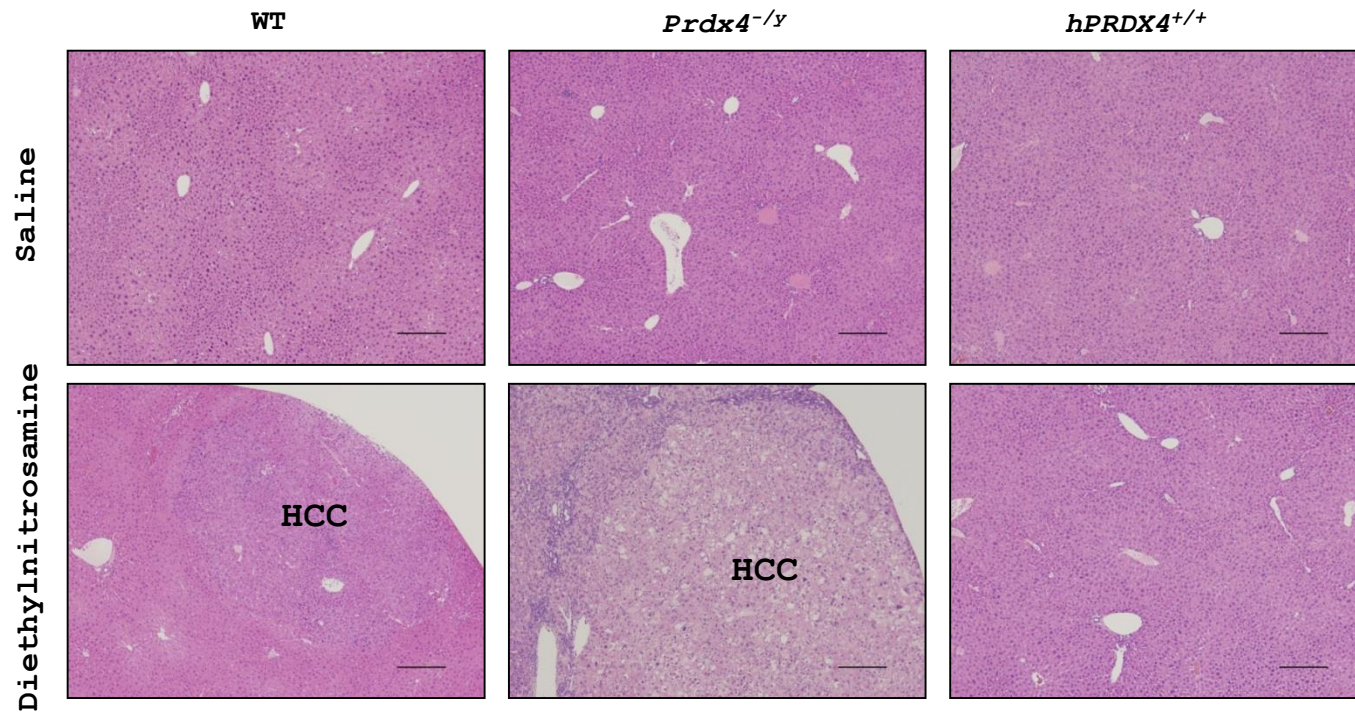
Animals and treatment



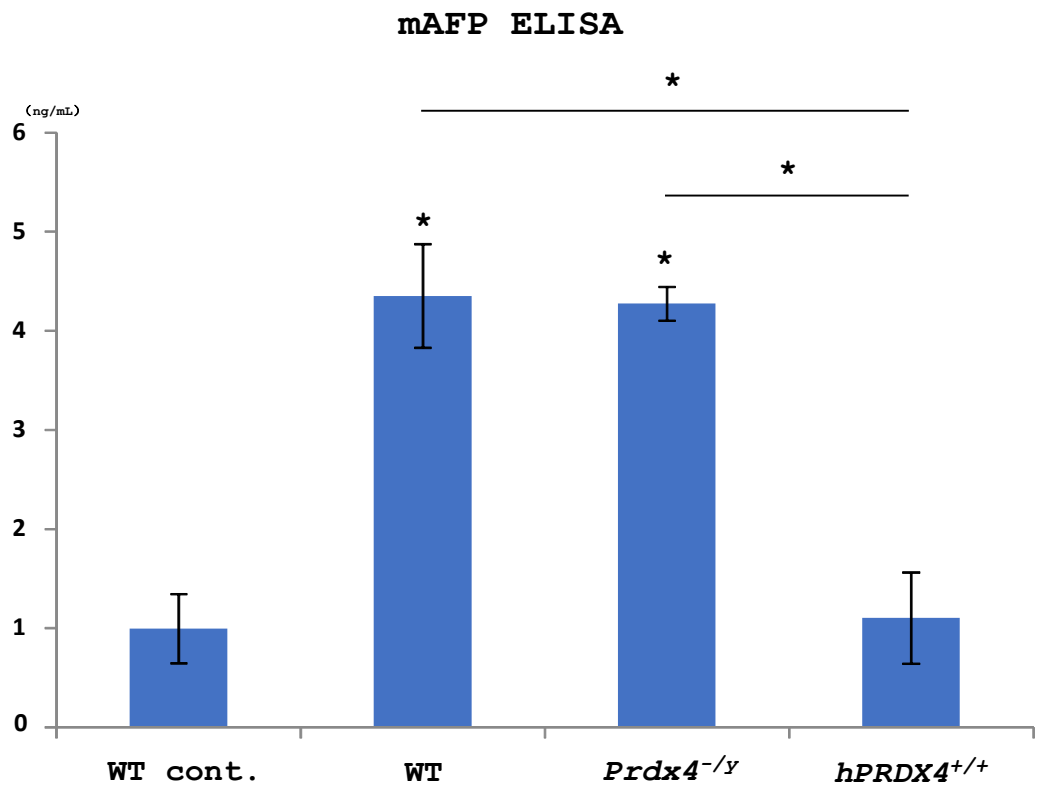
Rate of HCC development in WT, *Prdx4*^{-/y} and *hPRDX4*^{+/+} mice 25 weeks after DEN treatment or 24 months under natural condition

| | With tumor Number (%) | Tumor-free Number (%) | <i>P</i> |
|------------------------------|--------------------------|--------------------------|---------------|
| Saline-induced | | | |
| WT | 0(0) | 5(100) | |
| <i>Prdx4</i> ^{-y} | 0(0) | 5(100) | 1.0 |
| <i>hPRDX4</i> ^{+/+} | 0(0) | 5(100) | 1.0 |
| DEN-induced | | | |
| WT | 3(20) | 12(80) | |
| <i>Prdx4</i> ^{-y} | 12(80) | 3(20) | 0.0028 |
| <i>hPRDX4</i> ^{+/+} | 1(7) | 14(93) | 0.598 |
| Natural condition | | | |
| WT | 0(0) | 10(100) | |
| <i>Prdx4</i> ^{-y} | 3(43) | 4(57) | 0.0515 |
| <i>hPRDX4</i> ^{+/+} | 0(0) | 10(100) | 1.0 |

The average number of tumors in the liver of WT, *Prdx4*^{-/y} and *hPRDX4*^{+/+} mice treated with saline or DEN.



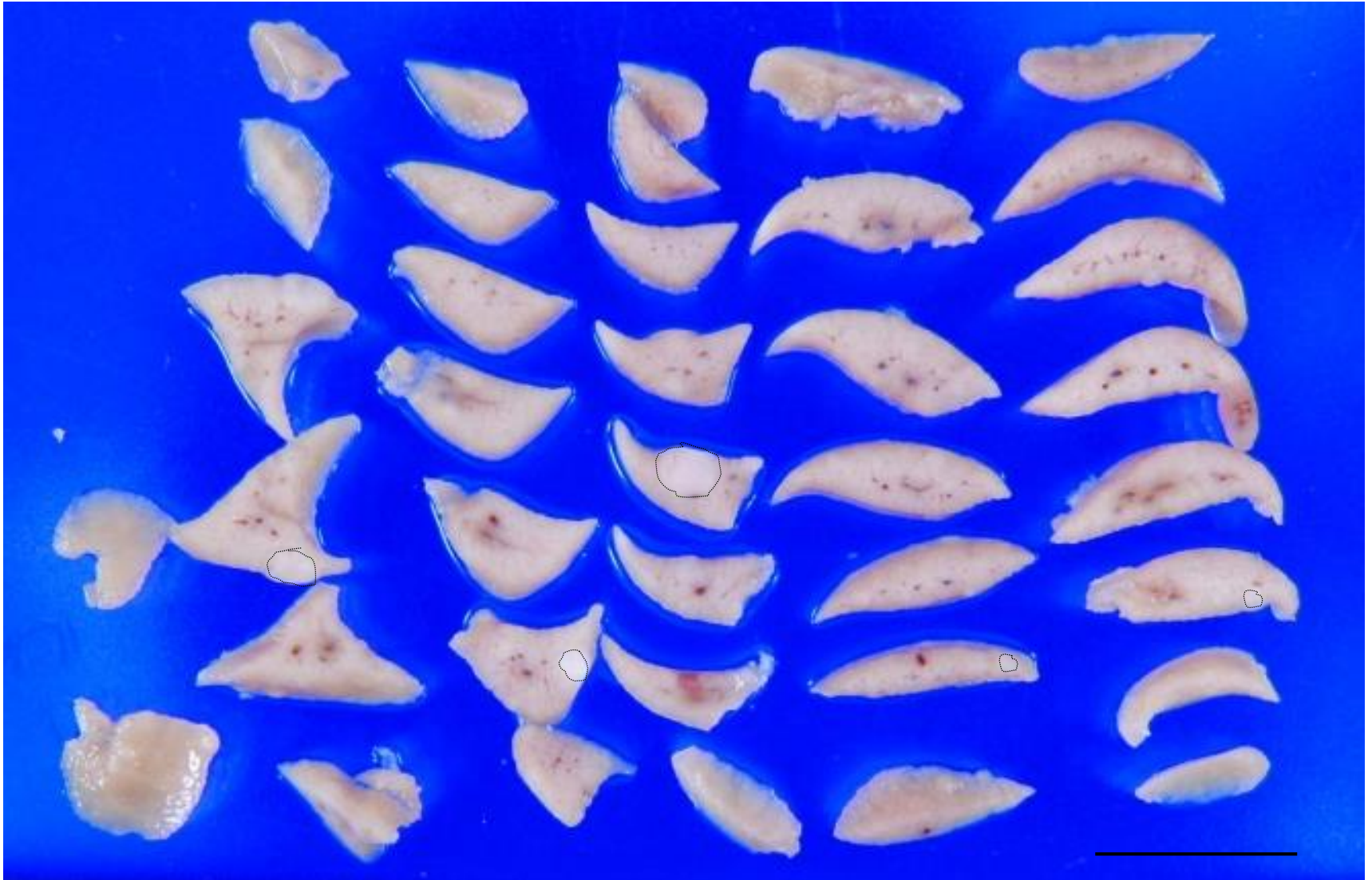
The serum mAFP levels of WT, *Prdx4*^{-/y} and *hPRDX4*^{+/+} mice after DEN treatment



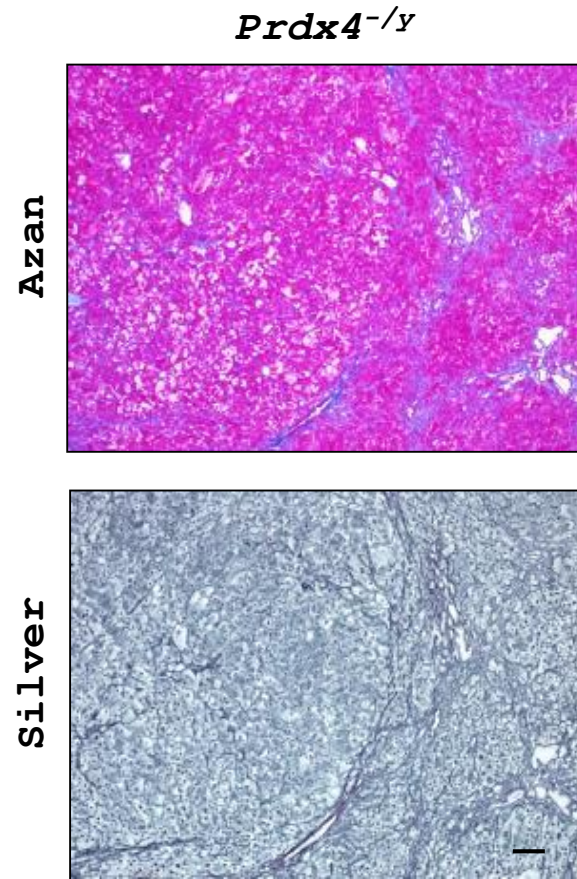
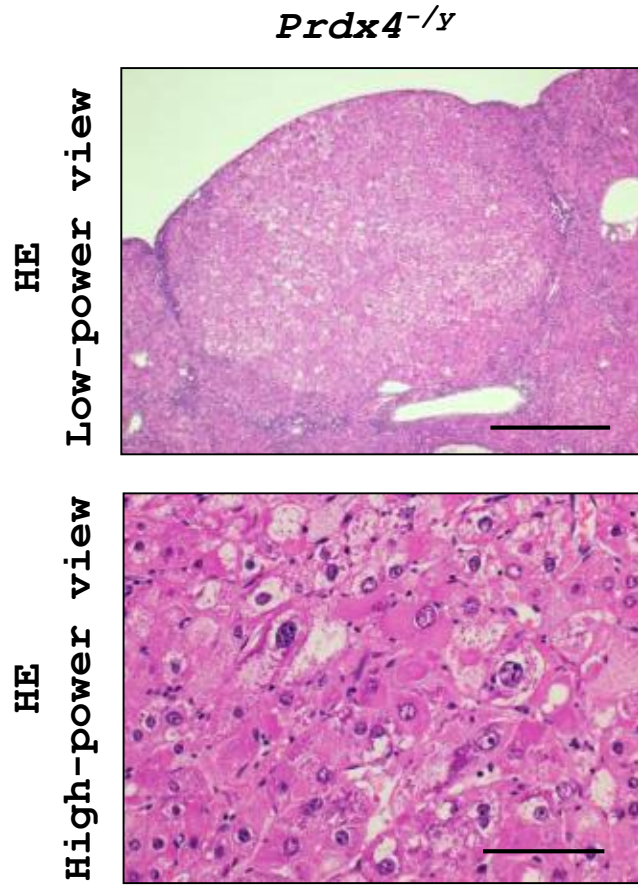
Multiple tumor nodules in the liver of *PRDX4^{-y}* mice after DEN treatment

Prdx4^{-y}

Gross



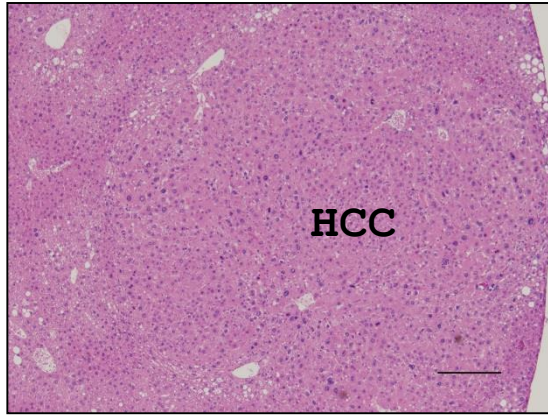
Hepatocyte tumors with the typical features of HCC



The incidence of HCC in the liver of 2-year-old *Prdx4*^{-/y} mice under natural conditions

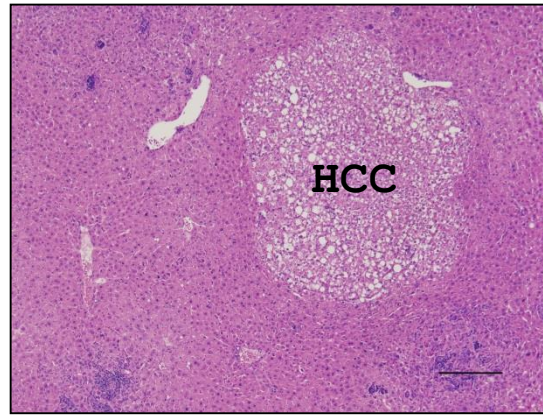
2-year old

Prdx4^{-/y}



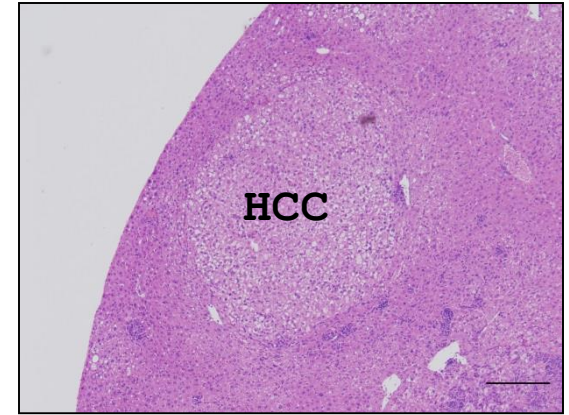
No. 3

Prdx4^{-/y}



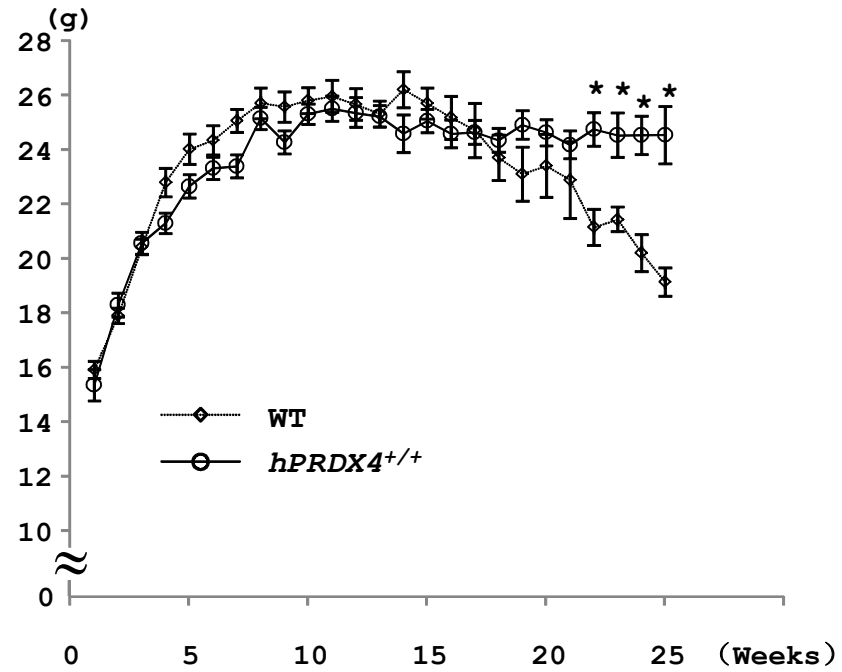
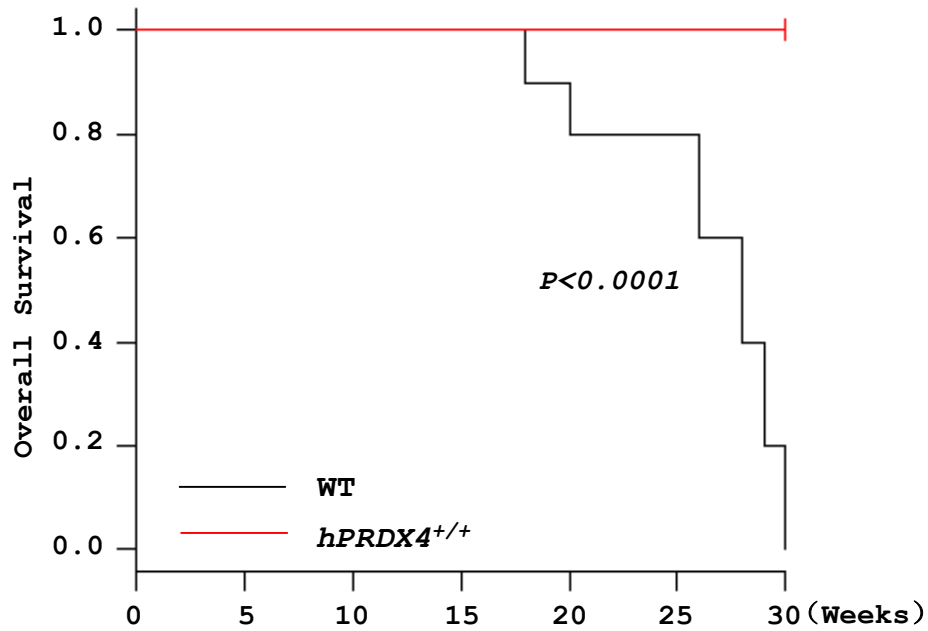
No. 4

Prdx4^{-/y}

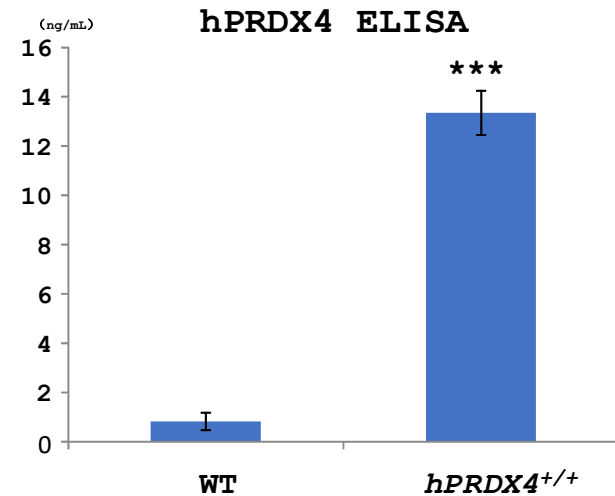
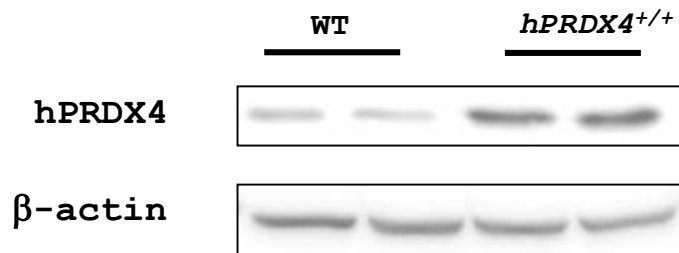
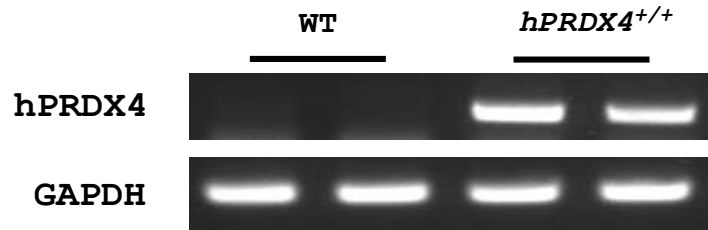
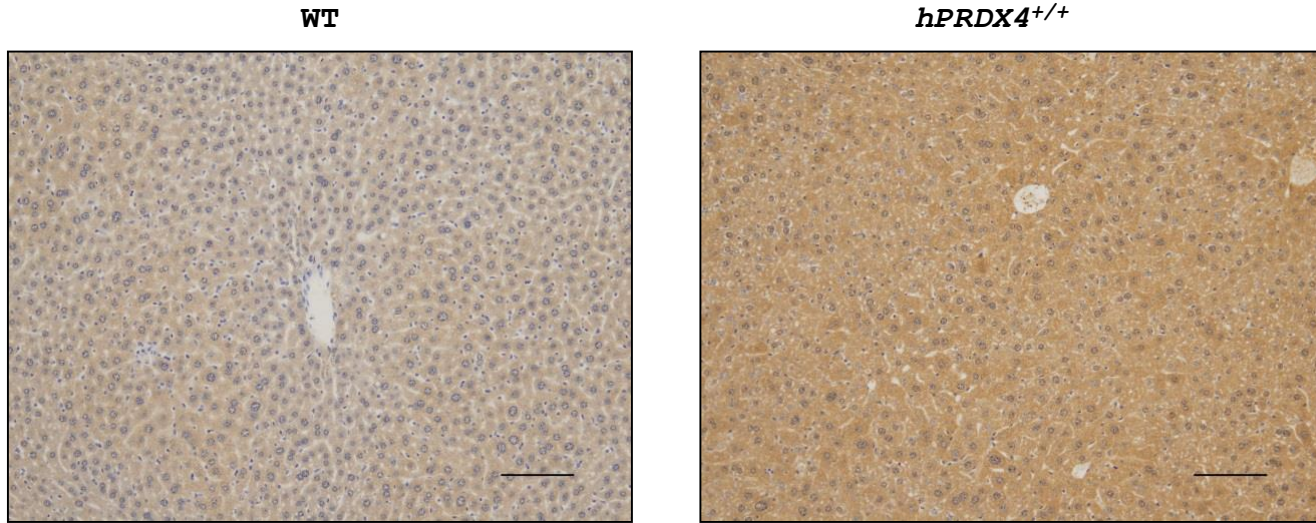


No. 6

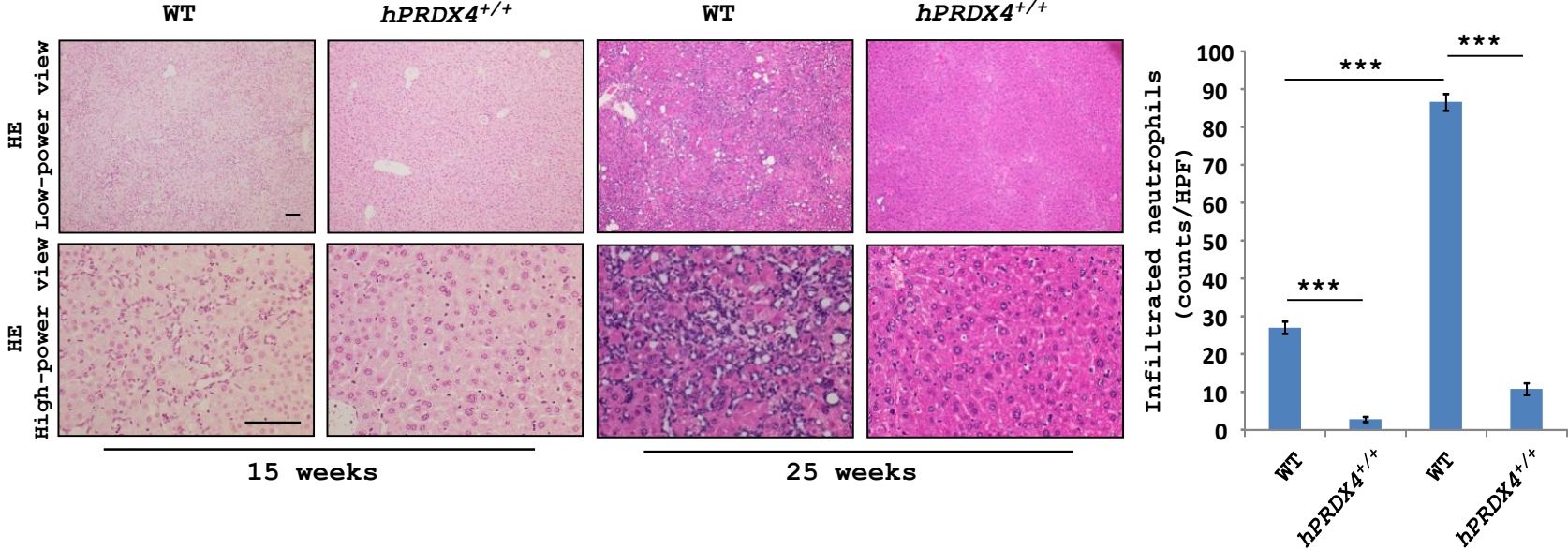
The survival and condition of DEN-treated mice



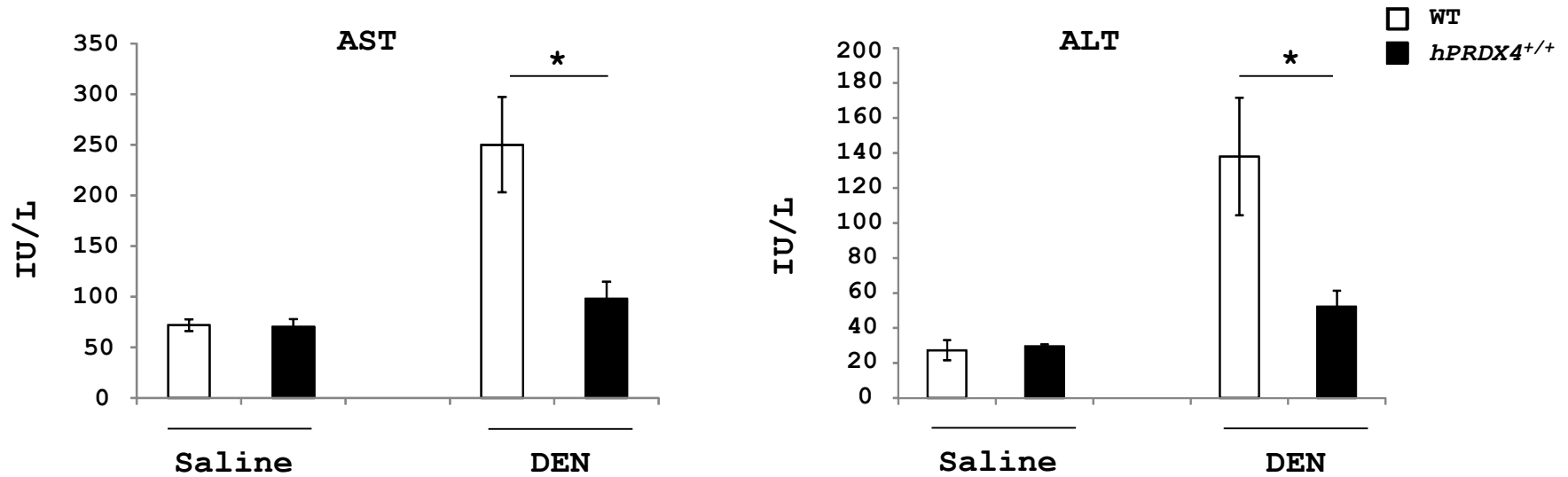
The expression of hPRDX4 in mice under basal conditions



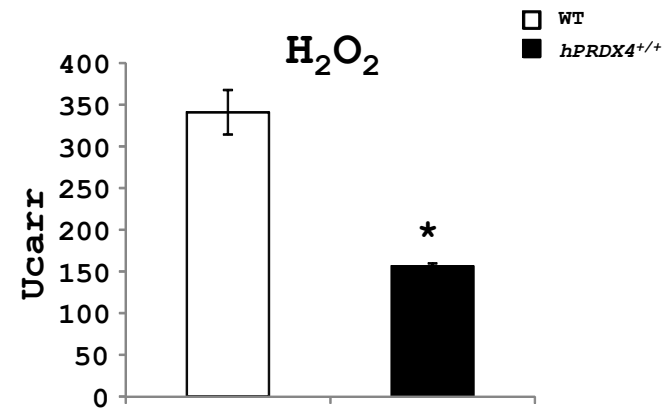
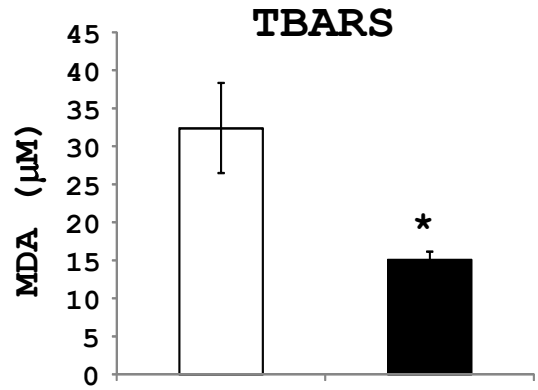
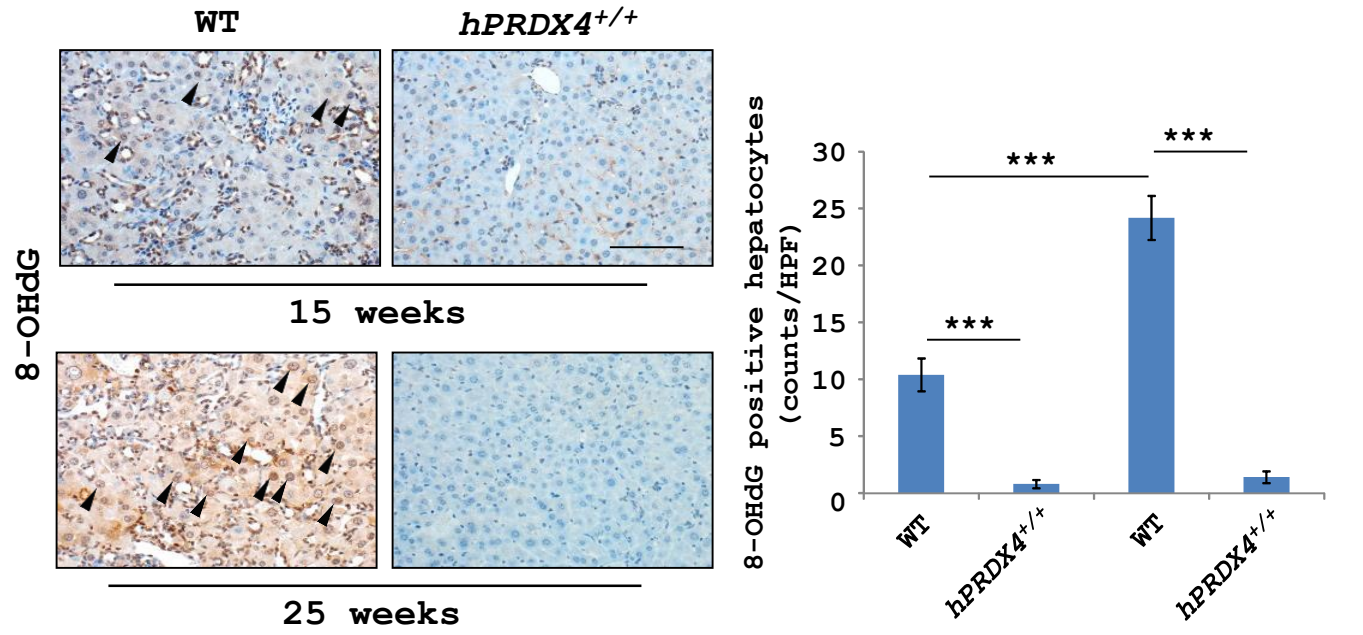
Infiltrated neutrophils in the liver of mice exposed to DEN



The levels of AST and ALT in the serum of mice exposed to DEN

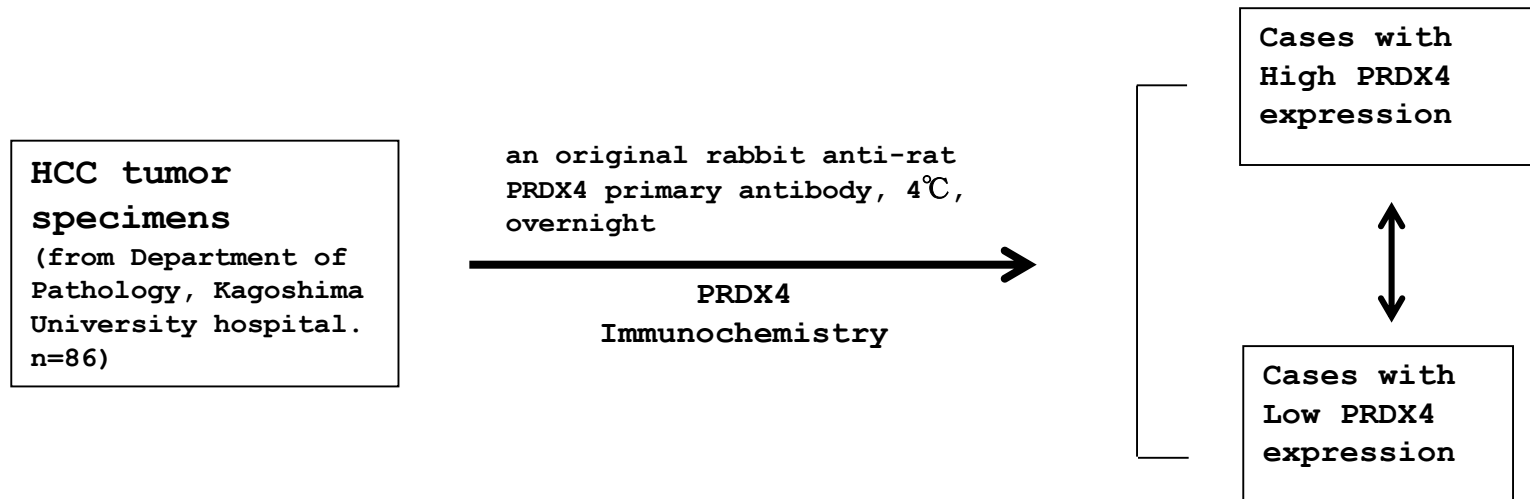


Oxidative stress in mice exposed to DEN



Method ②

Specimens from patients with HCC



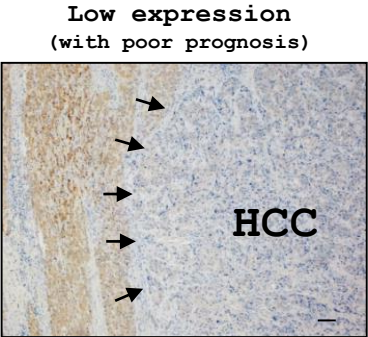
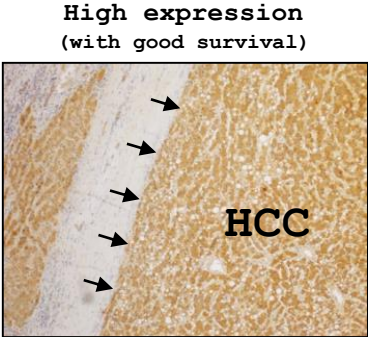
PRDX4 expression and clinicopathologic factors in patients with HCC

| | High expression (n=42) Number (%) | Low expression (n=44) Number (%) | <i>P</i> |
|-----------------------------|---|--|----------------|
| Age | 66.7 ± 1.7 | 69.0 ± 1.4 | 0.1536 |
| Gender | | | 0.909 |
| Male | 32 | 35 | |
| Female | 10 | 9 | |
| HBV | | | 0.247 |
| (+) | 7 | 13 | |
| (-) | 35 | 31 | |
| HCV | | | 0.29 |
| (+) | 21 | 16 | |
| (-) | 21 | 28 | |
| Child-Pugh grade | | | 0.615 |
| A | 37 | 36 | |
| B | 1 | 3 | |
| NA | 4 | 5 | |
| Tumor size (mm, mean SD) | 32.0 ± 2.9 | 58.2 ± 6.5 | 0.0003 |
| Number of tumors | | | 0.909 |
| single | 32 | 35 | |
| multiple | 10 | 9 | |
| Tumor differentiation | | | 0.675 |
| Well/moderately | 38 | 37 | |
| Poorly | 2 | 4 | |
| NA | 2 | 3 | |
| Capsular formation | | | 0.704 |
| (+) | 34 | 34 | |
| (-) | 8 | 10 | |
| Capsular invasion | | | 1 |
| (+) | 29 | 30 | |
| (-) | 5 | 4 | |
| Portal vein invasion | | | 0.046 |
| (+) | 8 | 17 | |
| (-) | 34 | 27 | |
| Hepatic vein invasion | | | 0.00952 |
| (+) | 5 | 17 | |
| (-) | 37 | 27 | |
| Hepatic artery invasion | | | 0.257 |
| (+) | 0 | 3 | |
| (-) | 42 | 41 | |
| Bile duct invasion | | | 0.137 |
| (+) | 0 | 4 | |
| (-) | 42 | 40 | |

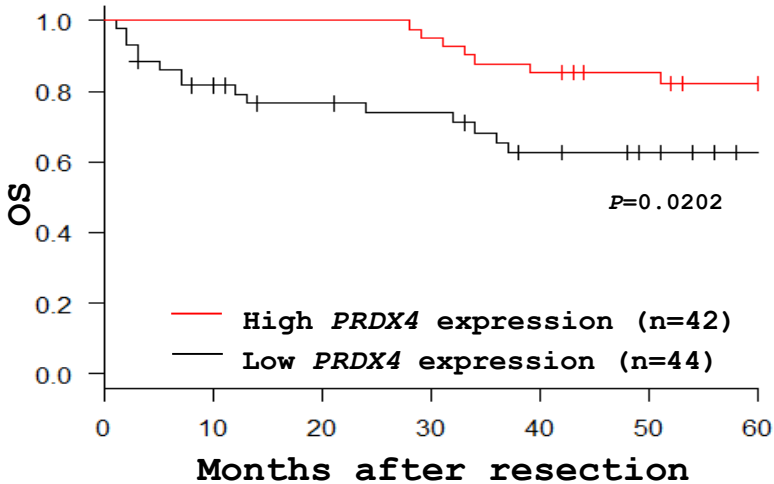
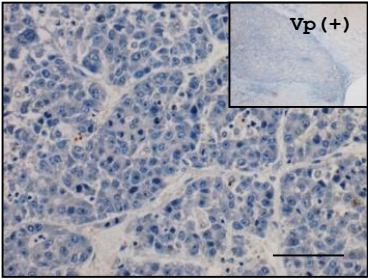
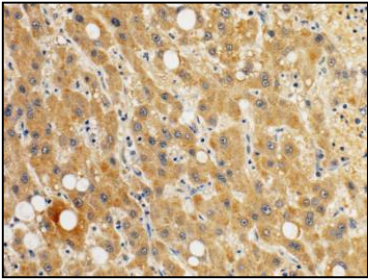
PRDX4 expression and overall survival in human HCC

PRDX4

Low-power view

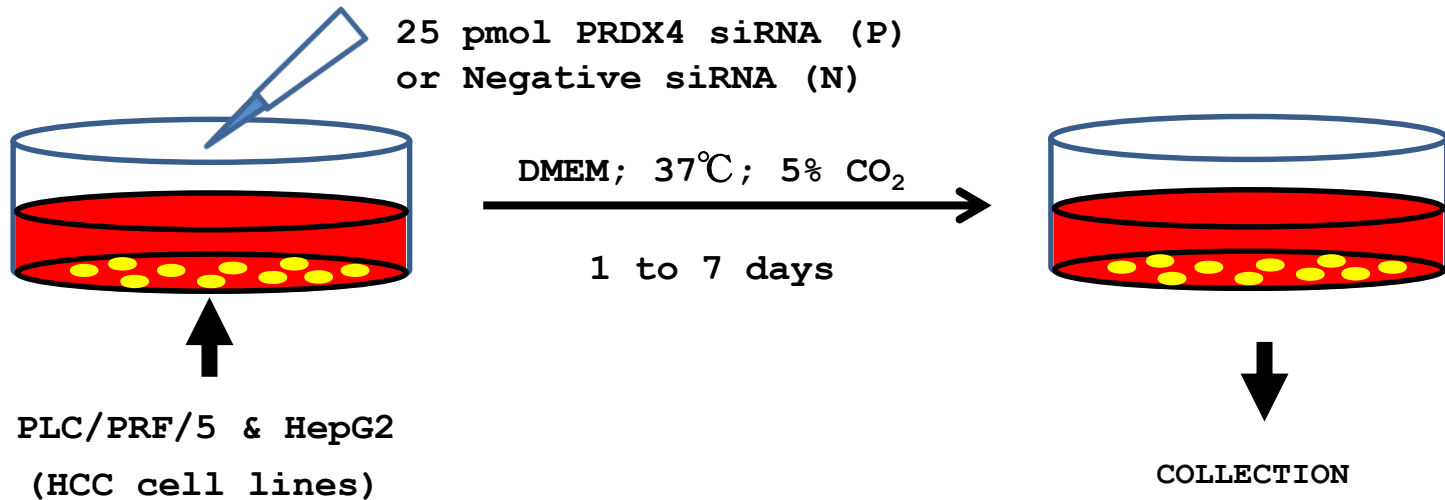


High-power view

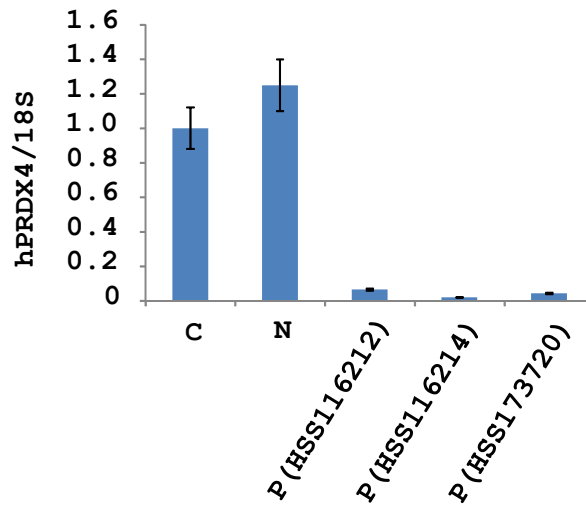


Method ③

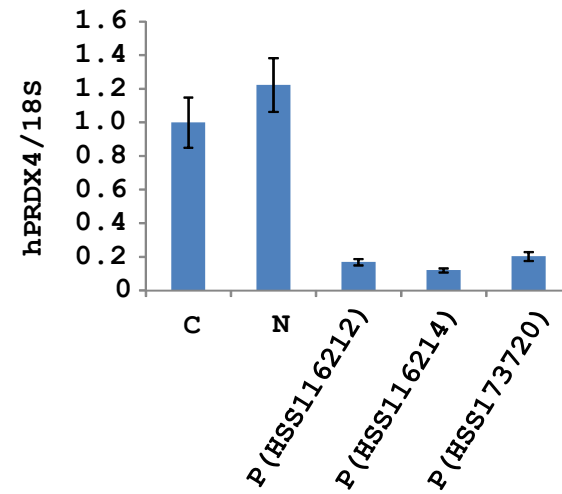
Cell culture and translation



PRDX4 expression in human HCC cell lines with siRNAs transfection ①

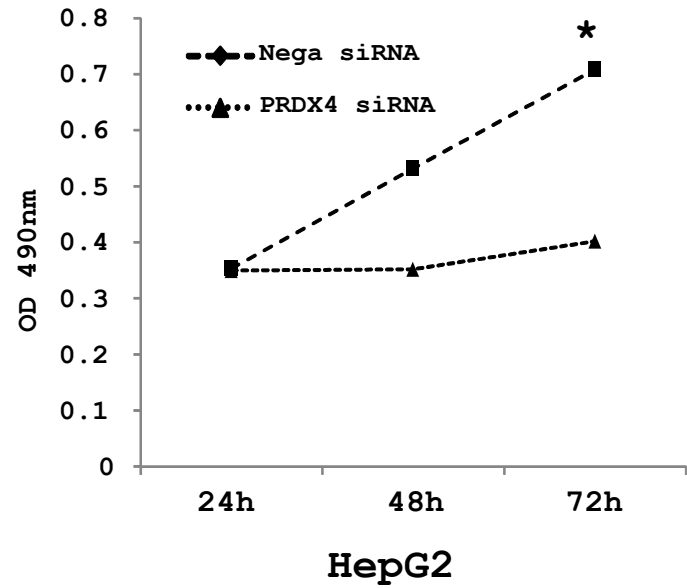
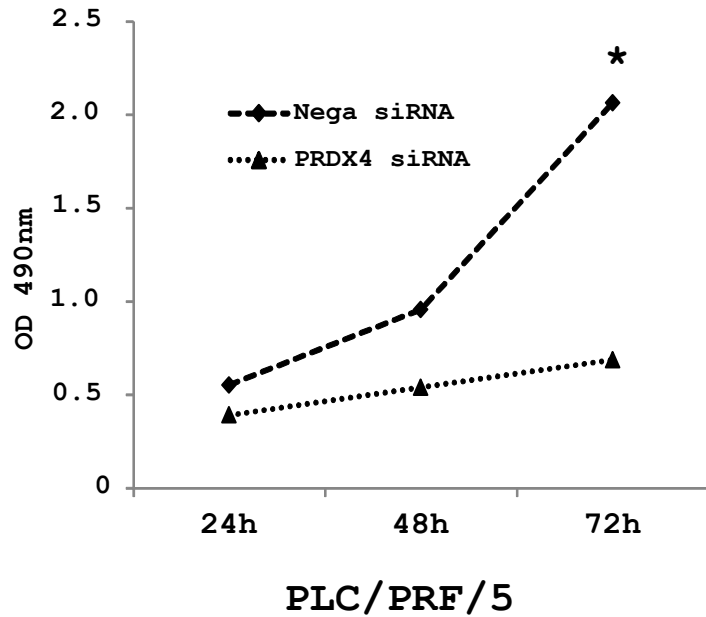


PLC/PRF/5

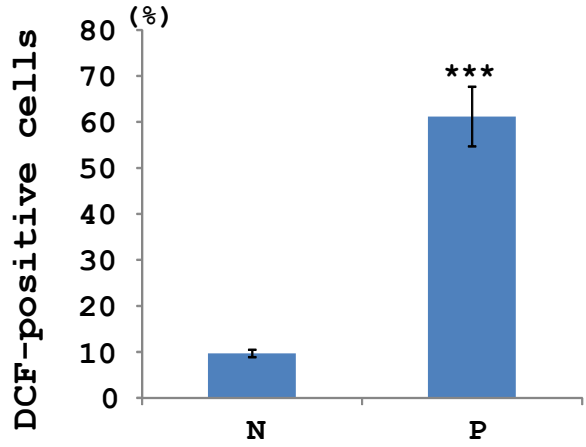
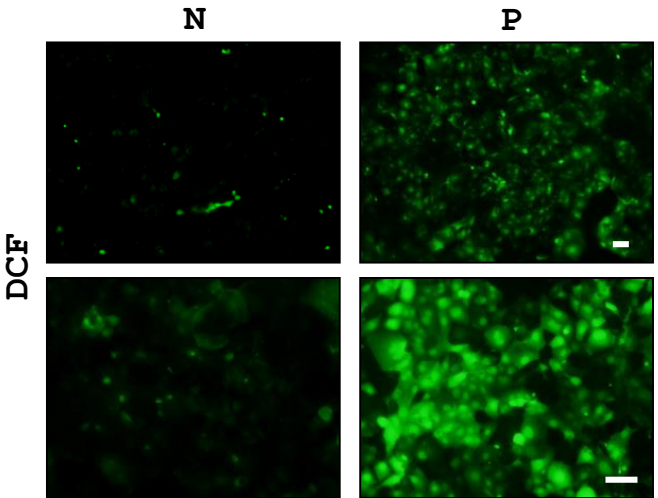
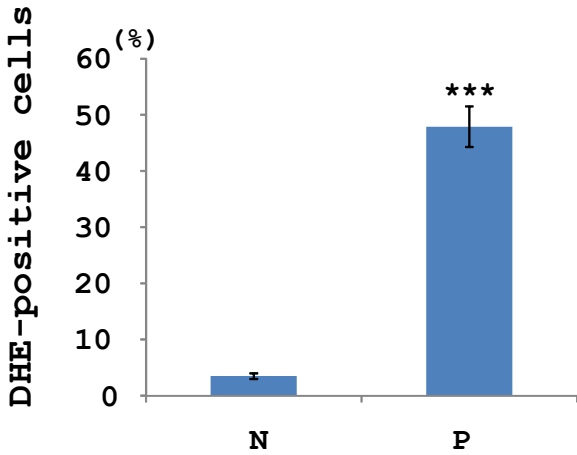
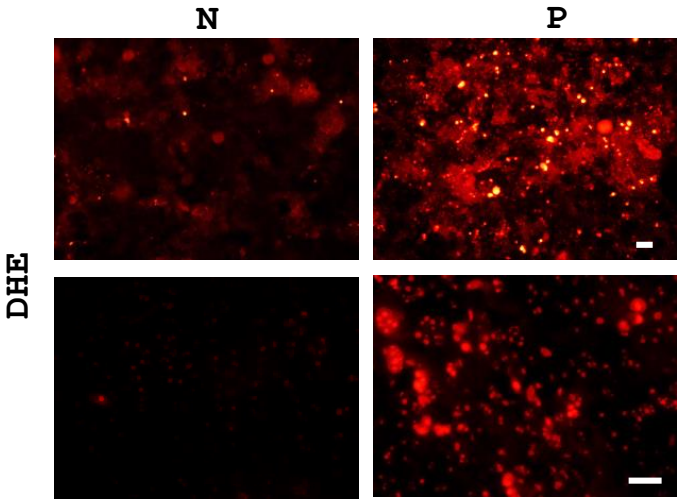


HepG2

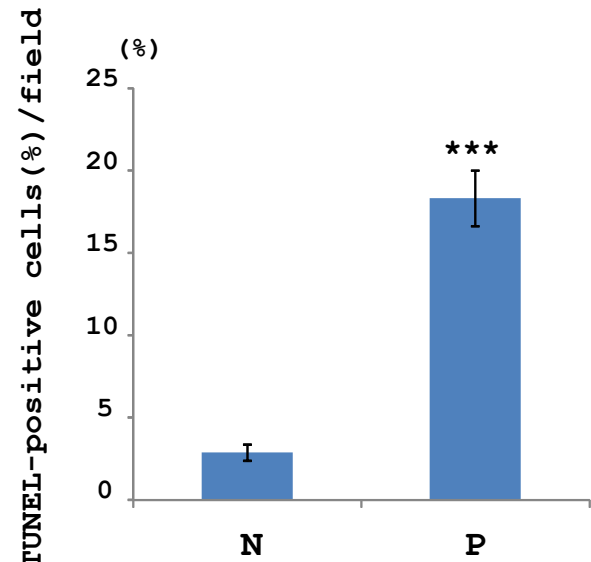
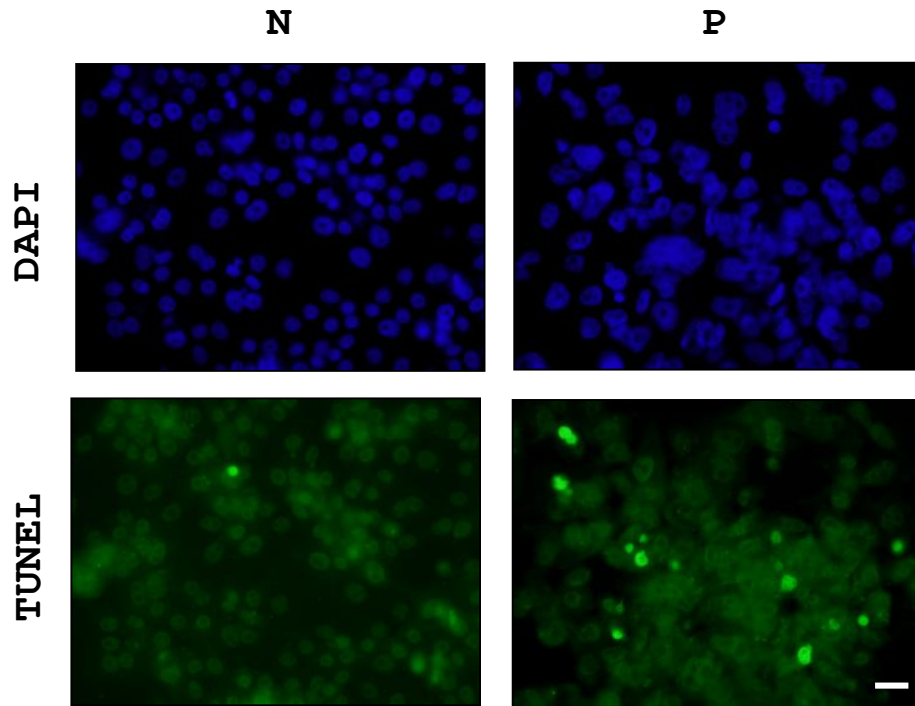
PRDX4 expression and proliferation in human HCC cell lines with siRNAs transfection



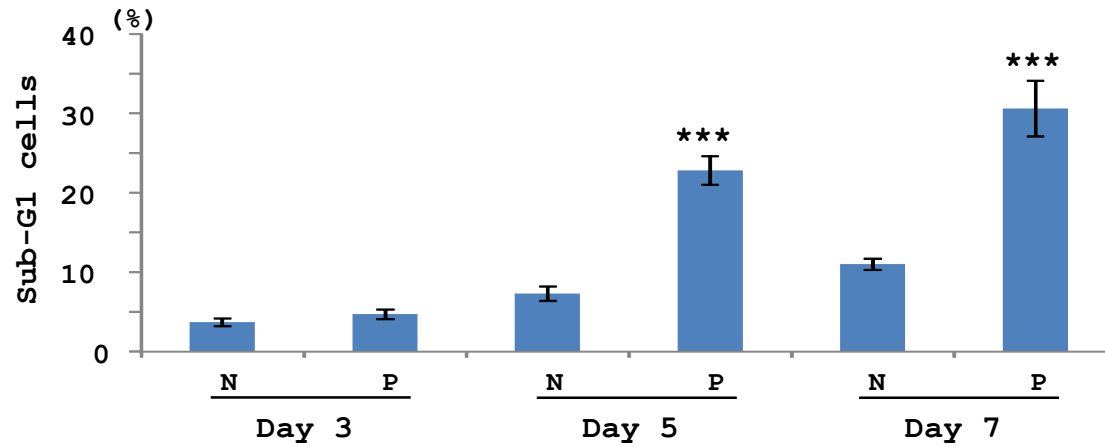
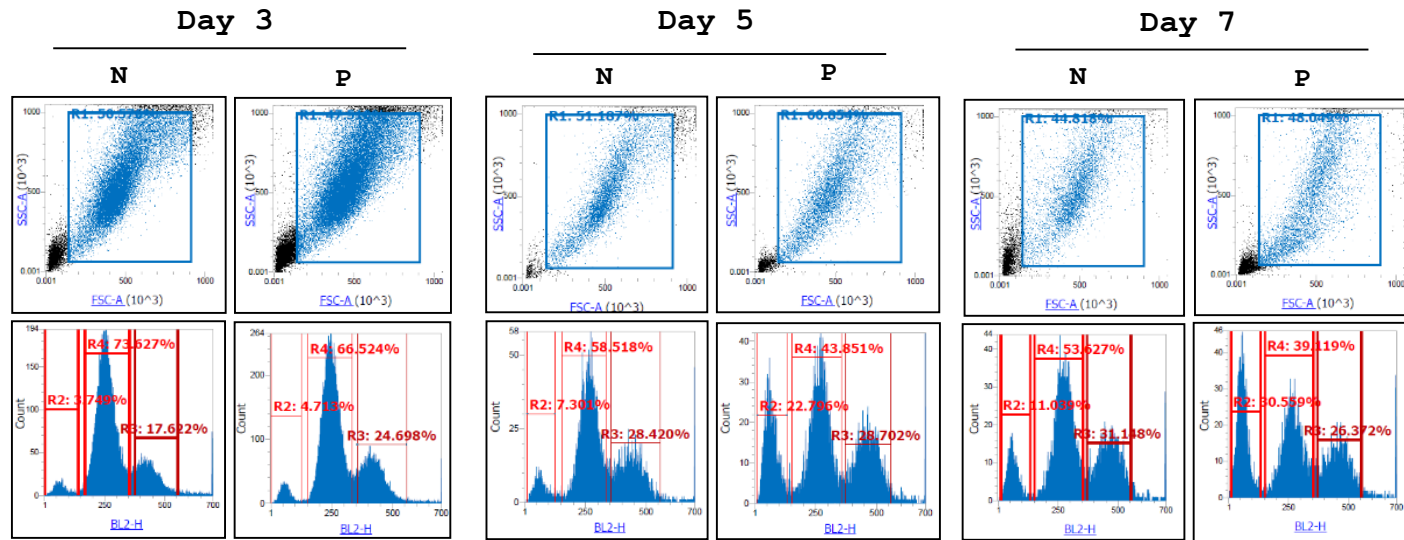
Oxidative stress in human HCC cell lines with siRNAs transfection



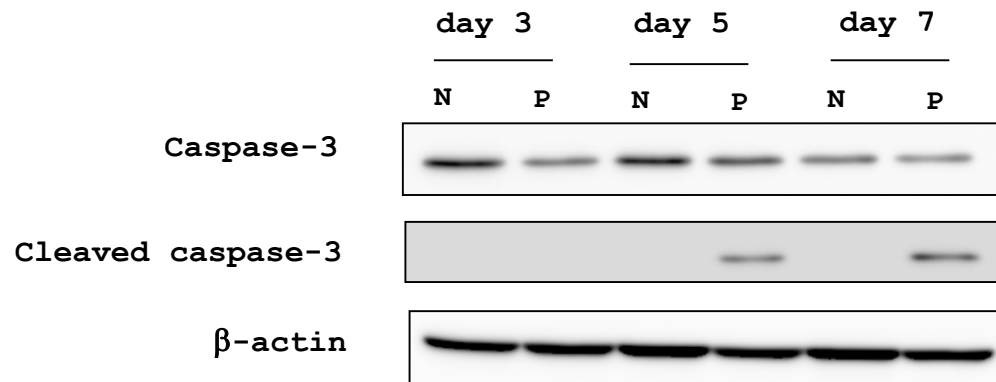
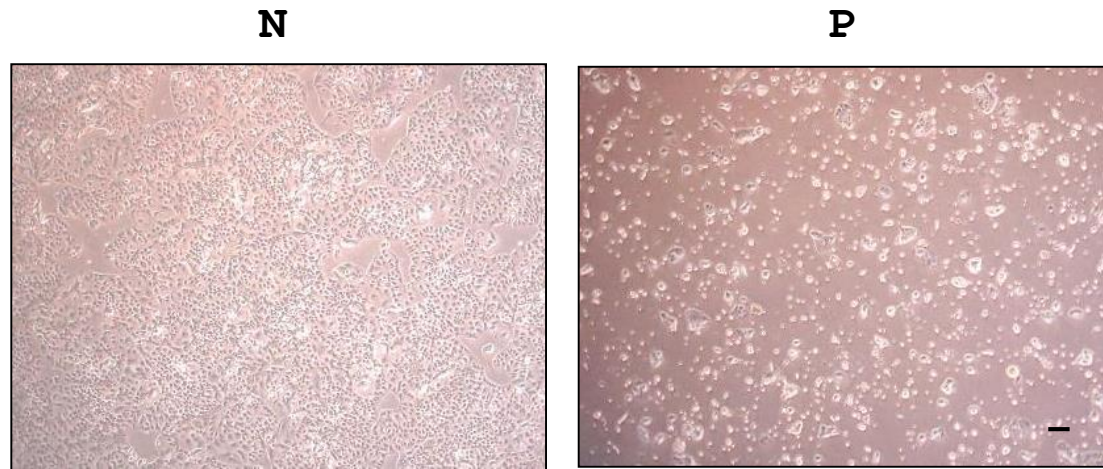
PRDX4 Knockdown induced cell apoptosis ①



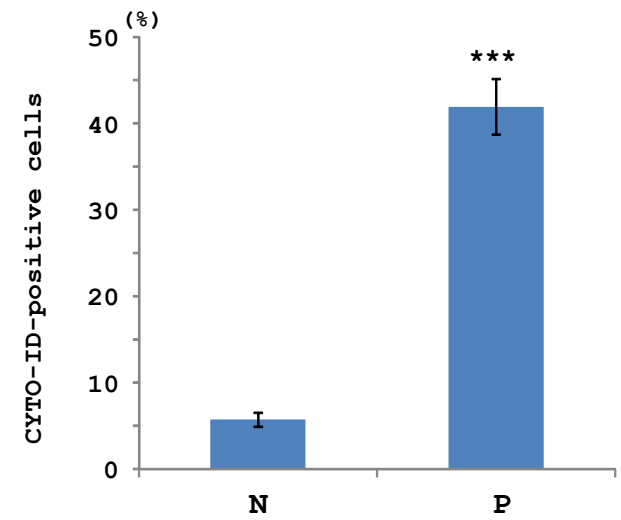
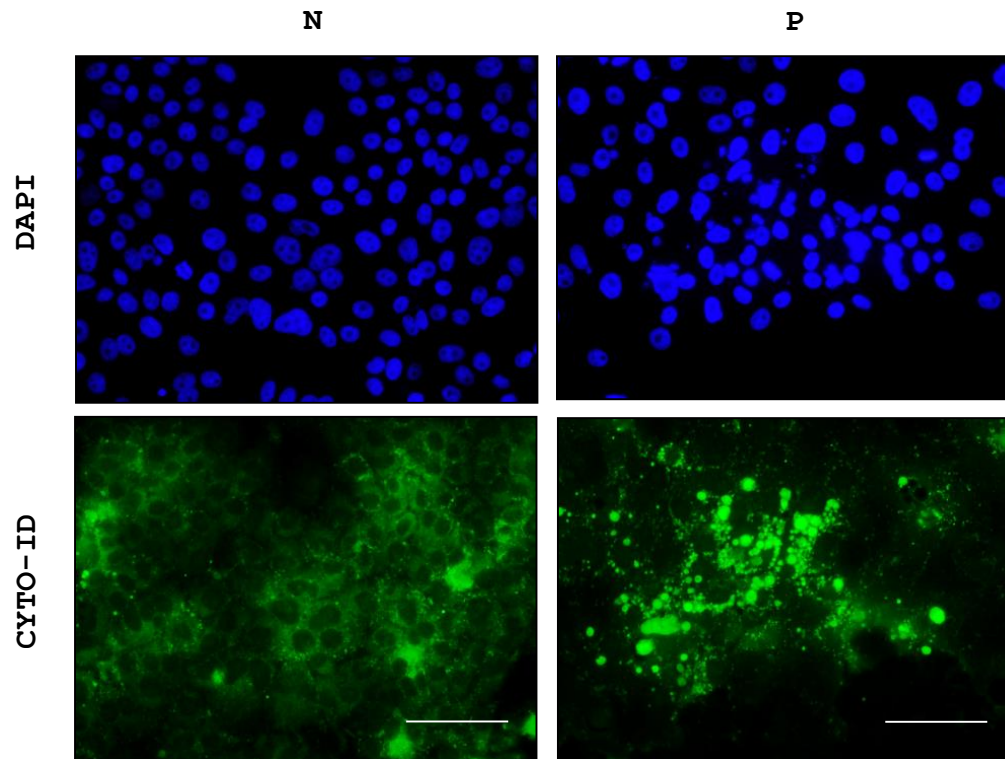
PRDX4 Knockdown induced cell apoptosis ②



PRDX4 Knockdown induced cell apoptosis ③

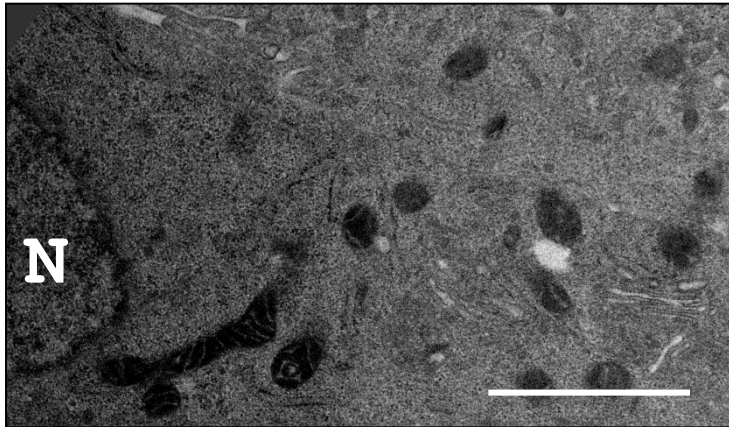


PRDX4 Knockdown induced cell autophagy ①

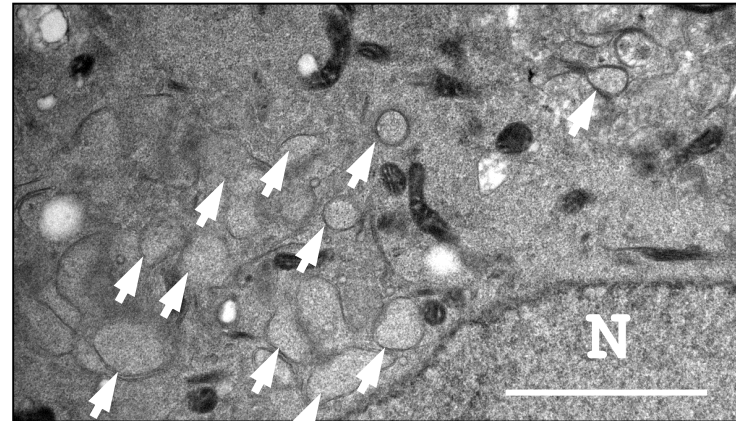


PRDX4 Knockdown induced cell autophagy ②

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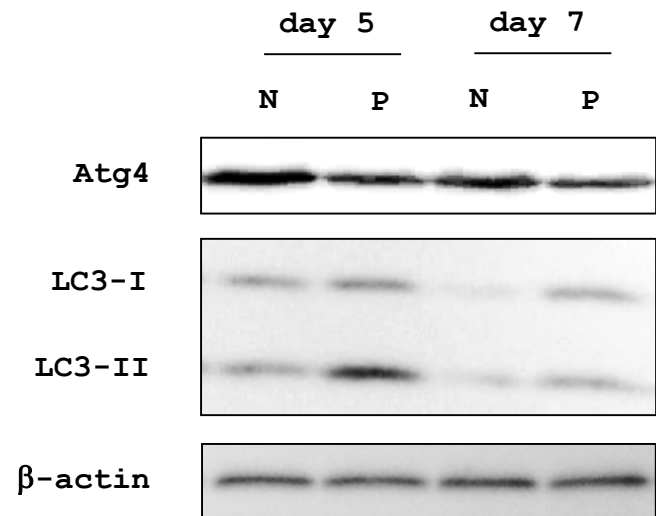
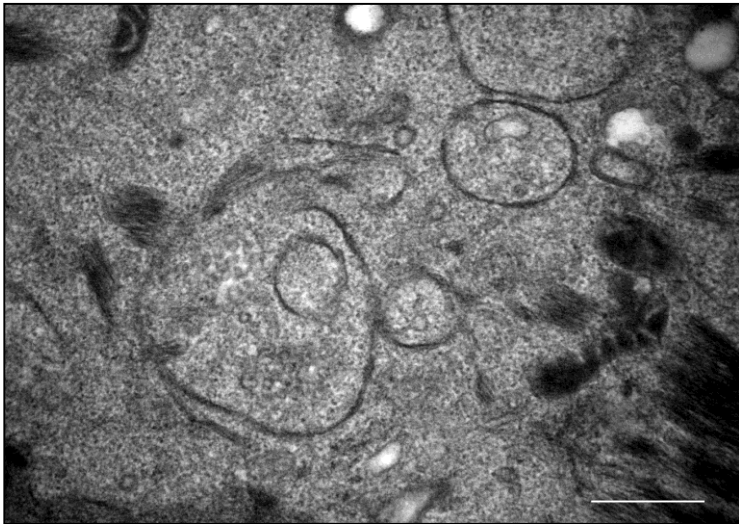


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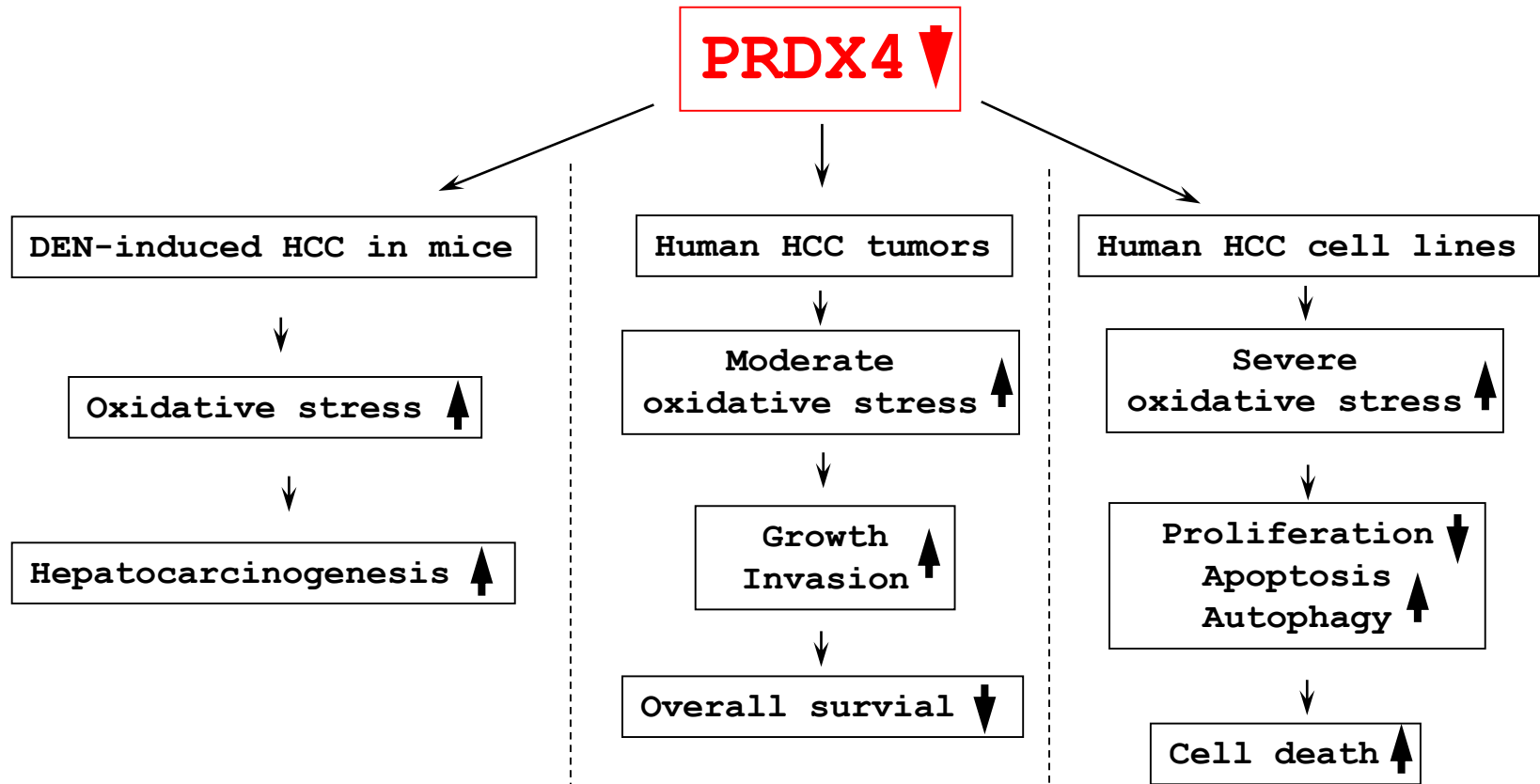


PRDX4 Knockdown induced cell autophagy ③

P



Schematic presentation



PRDX4: Preventer

Suppressor

Promoter

In vivo

In vitro

Conclusion

PRDX4 has an inhibitory effect in the initiation of HCC but a dual (inhibitory or promoting) role in the progression of HCC, suggesting the potential utility of PRDX4 activators or inhibitors as therapy for different stages and phenotypes of HCC.



Future studies

We would like to be in advance with regenerative medicine research connecting between HCC therapy (e.g., partial hepatectomy) and promising antioxidant enzyme PRDX4.