



# BDL model

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-SMC's CRO services-

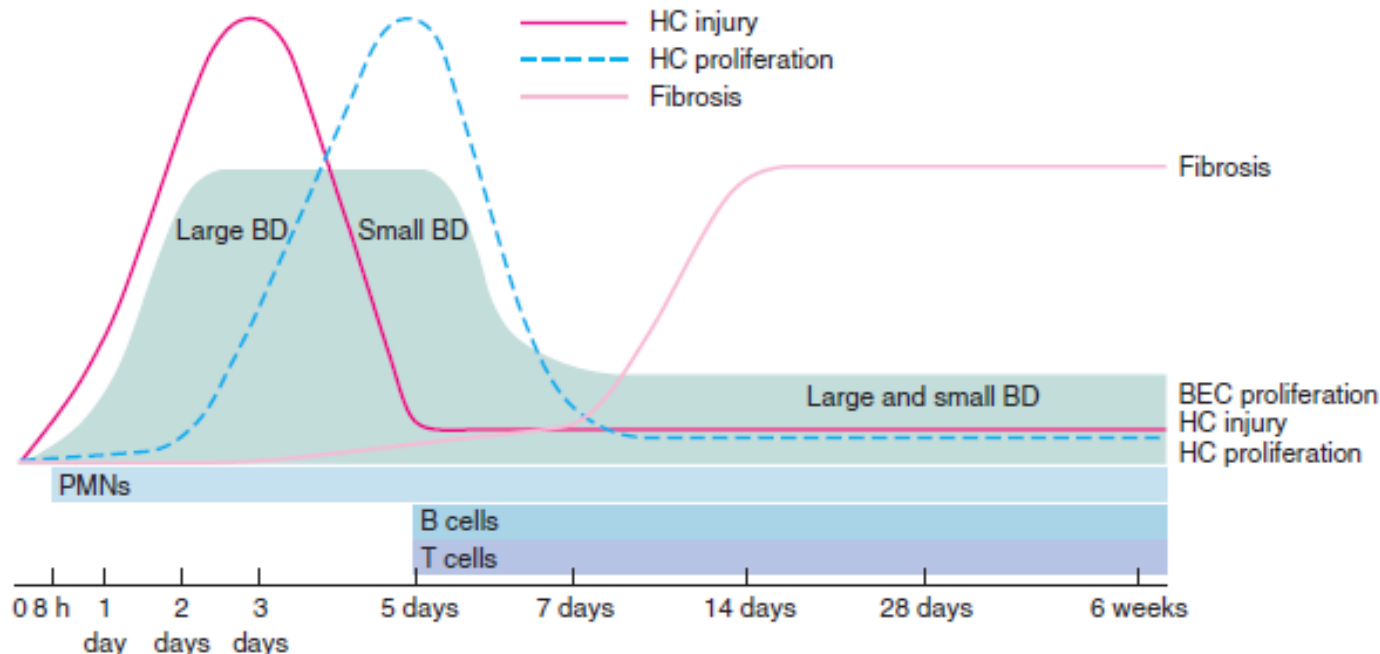
SMC Laboratories, Inc.

[smccro-lab.com](http://smccro-lab.com)



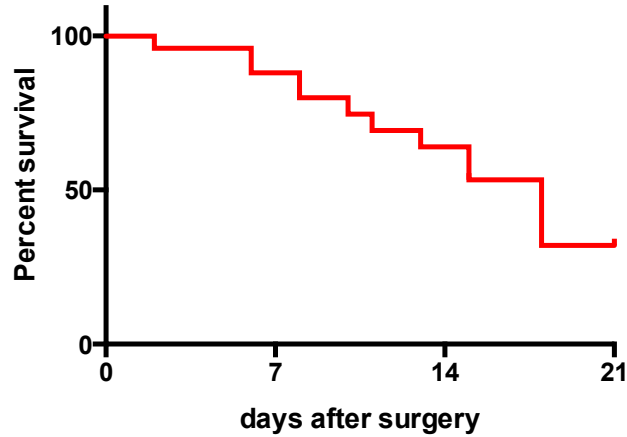
Model	Disease	Patterns of fibrosis	Period: From model induction to endpoint	ALT elevation	Possible mechanisms
<b>STAM™</b>	NAFLD/NASH/ Fibrosis/HCC	Central	9 week fibrosis 12 week fibrosis 20 week HCC	(+)	<ul style="list-style-type: none"> <li>● Low dose STZ induces mild diabetes with tissue injury.</li> <li>● Continuous HFD augments oxidative stress, inflammation, fibrosis and HCC.</li> </ul>
<b>CCl<sub>4</sub></b>	Fibrosis	Portal	4 week	(++)	<ul style="list-style-type: none"> <li>● Free radical metabolites alters the permeability of membranes.</li> </ul>
<b>MCD</b>	NAFLD/Fibrosis	Portal	12 week	(++)	<ul style="list-style-type: none"> <li>● Increased fatty acid uptake and oxidative stress, and decreased VLDL secretion.</li> </ul>
<b>BDL</b>	Cholestatic liver disease/PBC	Portal	1 week 3 week	(+++)	<ul style="list-style-type: none"> <li>● Mechanical cholestasis causes hepatocellular injury.</li> </ul>
<b>GVHR</b>	PBC	-	2 week	(+)	<ul style="list-style-type: none"> <li>● B6.T cell transfer to (B6.CH2bm12XB6)F1 induces GVHR and typical NSDC.</li> </ul>
<b>ConA</b>	AIH	-	24 hour	(+++)	<ul style="list-style-type: none"> <li>● T cell mitogen: T cell-mediated immune responses in the liver.</li> </ul>
<b>DDC</b>	PSC	Portal	4 week 8 week	(+++)	<ul style="list-style-type: none"> <li>● Induction of a reactive phenotype of bile duct epithelial cells and bile duct injury.</li> </ul>

**CCl<sub>4</sub>**: Carbon tetrachloride, **MCD**: Methionine Choline deficient, **BDL**: Bile duct ligation, **GVHR**: Graft-versus-host reaction, **ConA**: Concanavalin A, **DDC**: 3,5-diethoxycarbonyl- 1,4-dihydrocollidine, **STZ**: streptozotocin, **HFD**: high fat diet, **NSDC**: non-suppurative destruction cholangitis

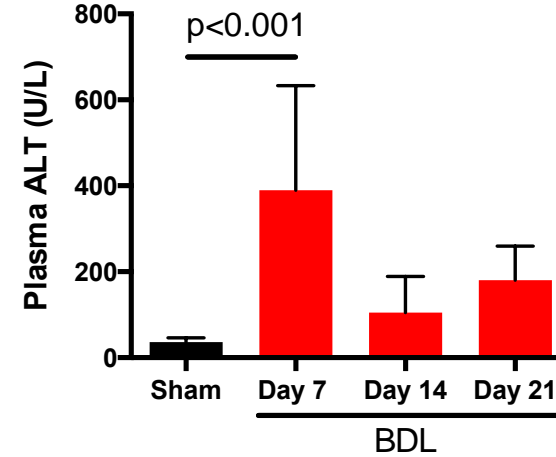


- Liver injury
  - Hepatocellular injury is detected within 5 days after BDL
  - Hepatocellular proliferation occurs after acute liver injury
- Inflammation
  - Neutrophils migrate into the liver 8h after BDL
  - T and B cells are observed at portal tract 5 days after BDL
- Fibrosis
  - Cholangiocellular proliferation is apparent before collagen deposition
  - Collagen deposition is visible after 7 days and continued to progress

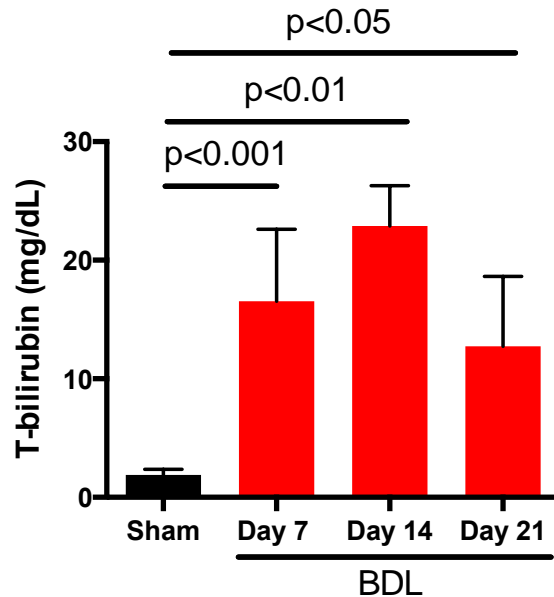
## ■ Mortality rate



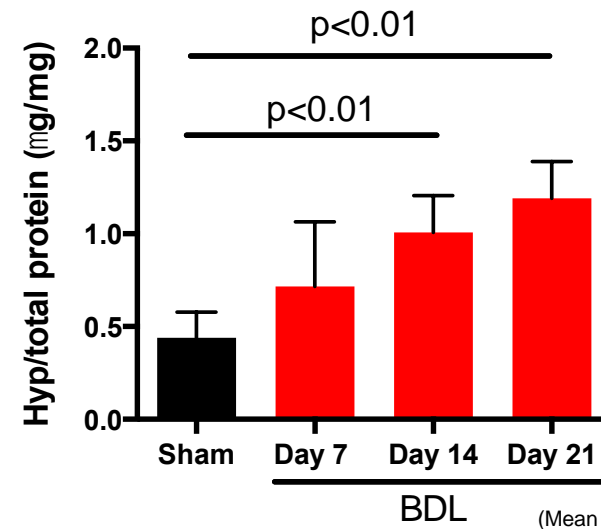
## ■ Plasma ALT levels



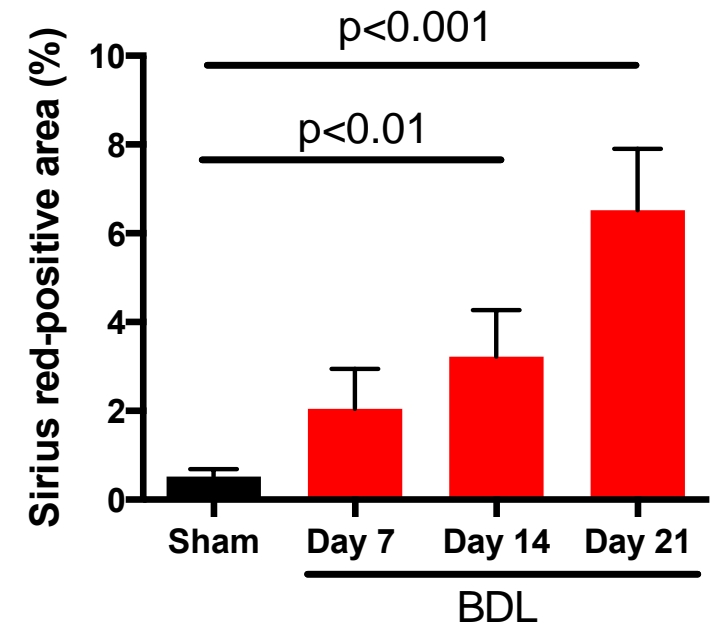
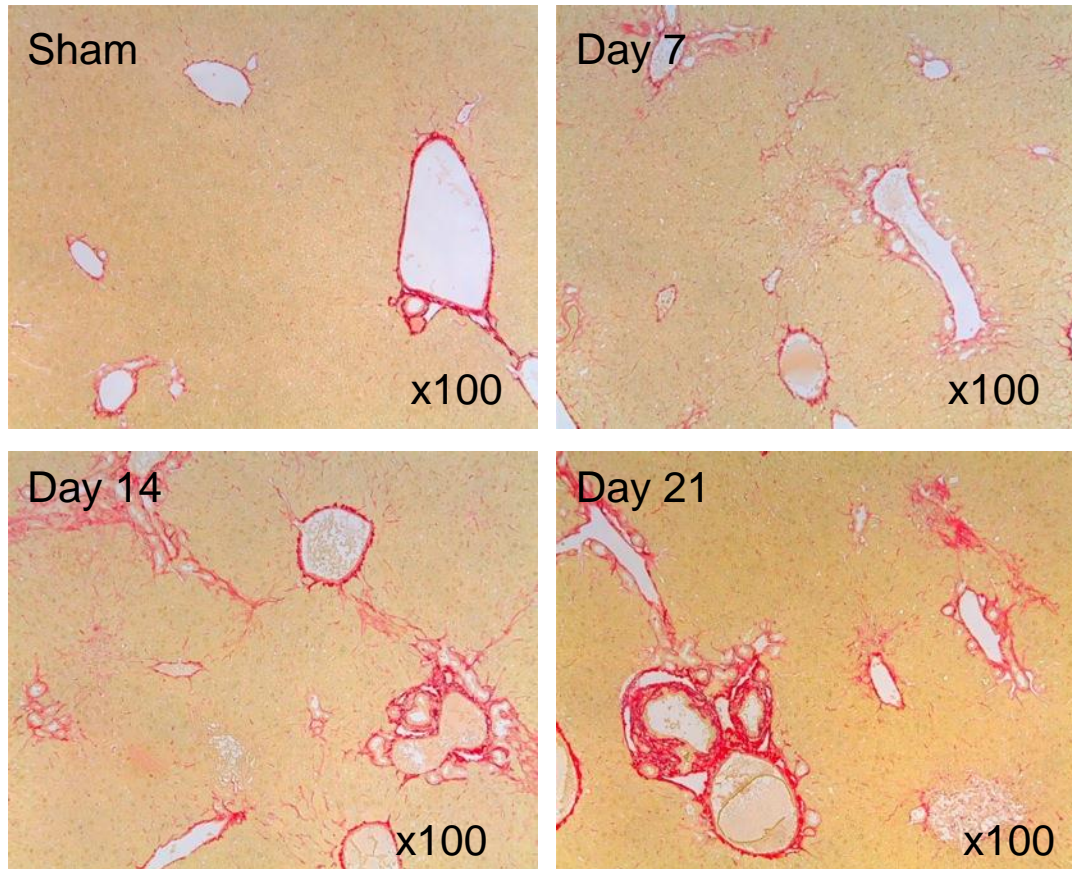
## ■ Plasma total bilirubin levels



## ■ Liver hydroxyproline content

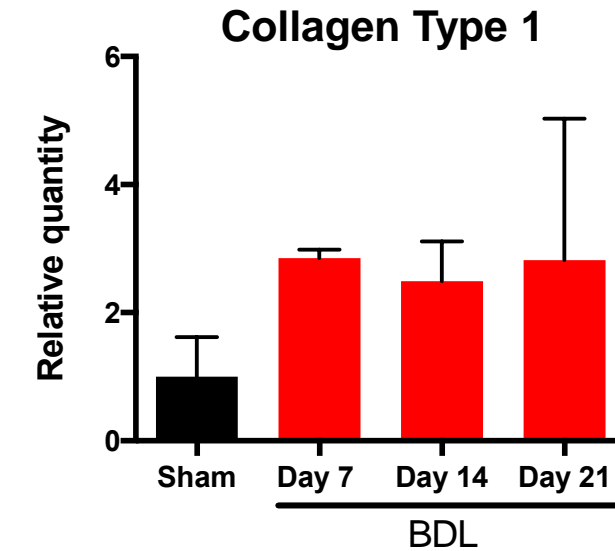
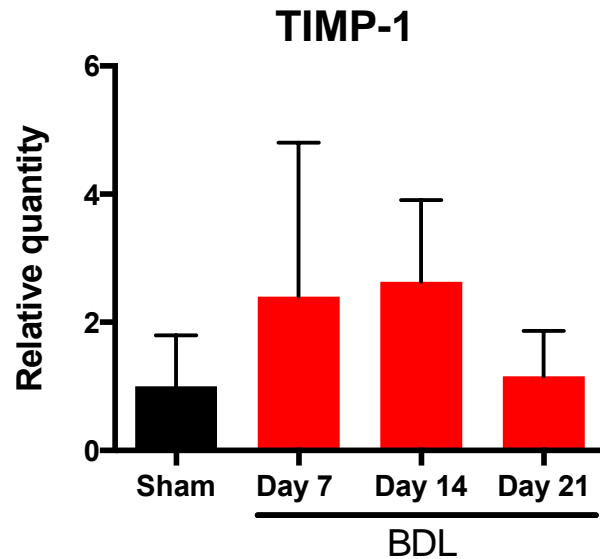
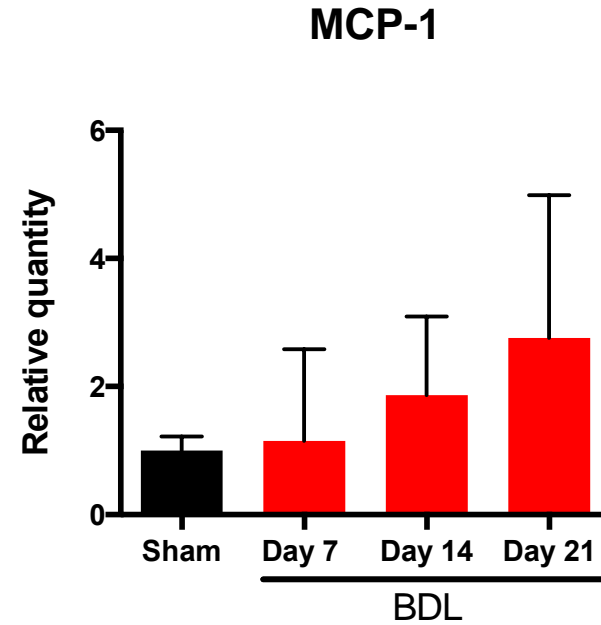
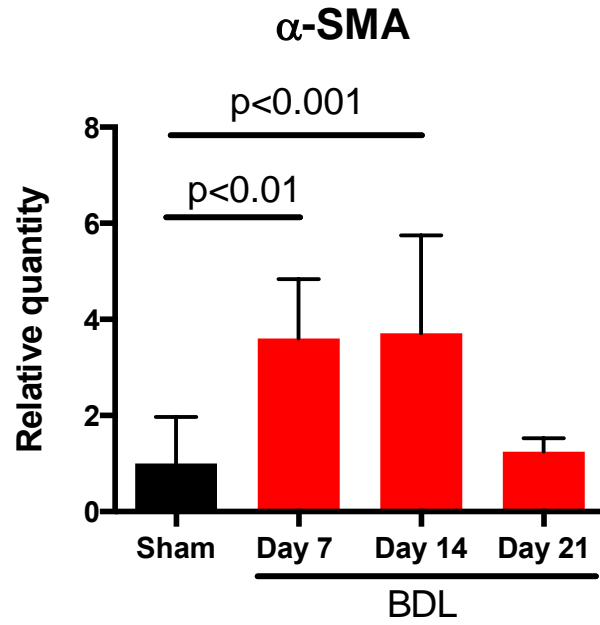


## ■ Representative microphotographs SR-stained liver sections

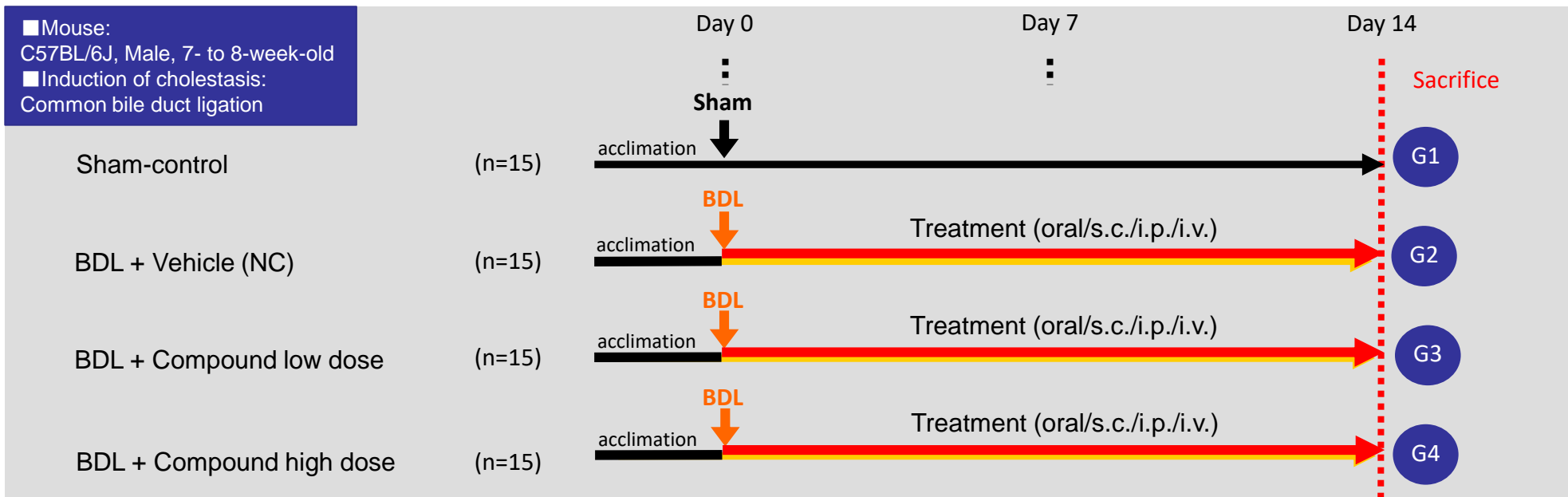


(Mean ± SD, n=3 - 5)

- Collagen deposition and ductal proliferation are visible 7 days after BDL
- Sirius red-positive area is increased about 20-fold by Day 21

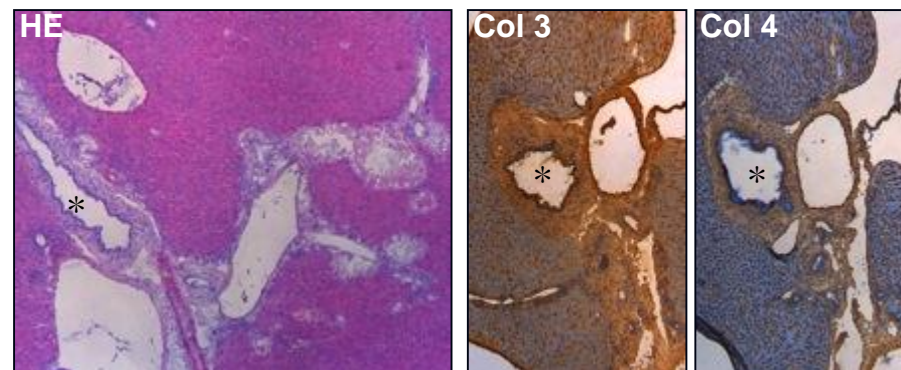


# Study plan for assessing effects of compounds in BDL-induced CLD model in mice



## Study design

- Arm: 4  
Control, Vehicle, Test substance x 2 doses
- The number of mice/group before dosing: n=15
- Baseline: Day 0 (just prior to BLD)
- Randomization: Body weight at Day 0
- Treatment period: 2 weeks
- Endpoints (Day 14):
  - Fibrosis area (SR)
  - <Analytical items>
  - Plasma/Serum: T-Bil, ALP
  - Liver hydroxyproline content
  - Gene expression in the liver
  - Immunohistochemical staining
  - Survival rate



bile duct

**BDL:** Bile duct ligation, **oral:** oral administration, **s.c.:** subcutaneous injection, **i.p.:** intraperitoneal injection, **i.v.:** intravenous injection, **NC:** Negative Control