SMC Laboratories,Inc.

BDL model

~Cholestatic liver disease model~

Summary version

The **full version** includes the following content.

- Comparison table of human and BDL model
- Disease state time course data
- Additional histology and gene expression data

etc.

Request for the full version material from here.

SMC Laboratories – Non-clinical CRO based in Tokyo

SMC Labroratories:

A pharmaceutical research assistance firm that provides drug evaluation studies to universities and R&D companies enthusiastic about delivering novel drugs to patients suffering from unmet medical needs. We focus on fibrosis, and support development of novel drugs by providing preclinical drug efficacy study services all around the world with the following disease animal models. We provide preclinical drug efficacy study services with our proprietary model, STAM™, inflammatory and fibrotic disease models (standard models), and disease models established at clients' requests custom models).

Proprietary models	Standard models	Custom models
♦MASH model - STAM™ ♦ HCC models - STAM™	【Liver】 ♦Liver fibrosis model - CDAHFD model - CCl_4 model (Cirrhosis) ♦ HCC models - DEN + CCl4 model *Total 8 models*	♦ Acute Liver Failure model - APAP ♦Xenograft model (Orthotopic)
UNDER CONSIDERATION	【Lung】 ♦IPF - Bleomycin-induced model ♦COPD model - PPE model *Total 4 models*	♦ALI model - LPS model
	【Skin】 ♦SSc/SSc-ILD model - Bleomycin skin fibrosis model (with Interstitial lung disease)	♦ Psoriasis model - Imiquimod (IMQ)-induced dermatitis model
We are constantly developing models that are needed!	【Kidney】 ♦CKD models - UUO model - Adenine model - Adriamycin model - Folic Acid model	♦ PKD model - pcy mouse model
	【Colon】 【Brain】 【Others】	【Others】

15 successful CTA packages

Over **600** MoAs tested

Total **20** models focused on inflammation, fibrosis and cancer

Experienced in more than **1,000** studies

Establishing **18** new models

78% success rate

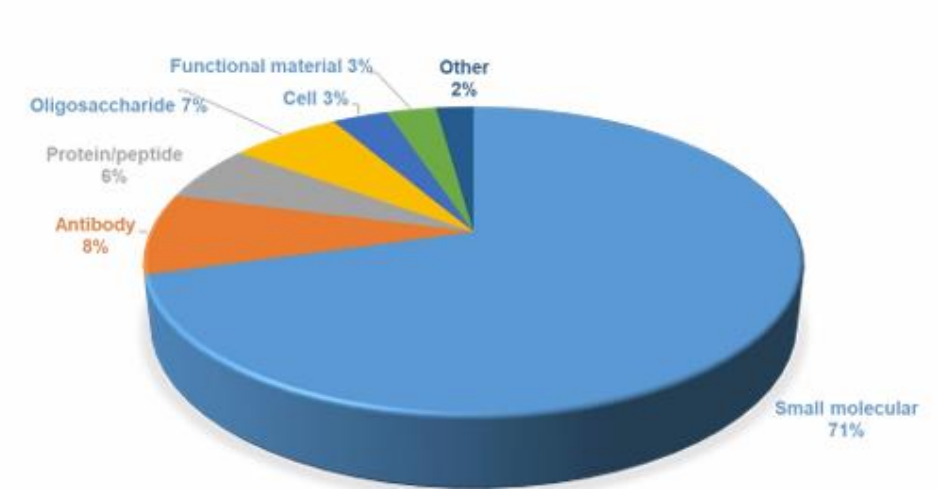
SMC overview

- Established in 2014
- Clients from 30 countries
  - Oversea clients : 70%
  - **# of clients: Over 1,200**
  - Repeat rate: 90%
  - Average # of trials: about 3 studies / client

We are experts in the field of liver disease

Experience with Modalities

SMC Laboratories has liver fibrosis models with various indications, including MASH-fibrosis (STAM GAN diet), Cholangitis models (BDL,DDC), and liver fibrosis models (MCD, CDAHFD, CCl4, WD + CCl4). The number of test articles evaluating drug efficacy using these models exceeds 1,000.



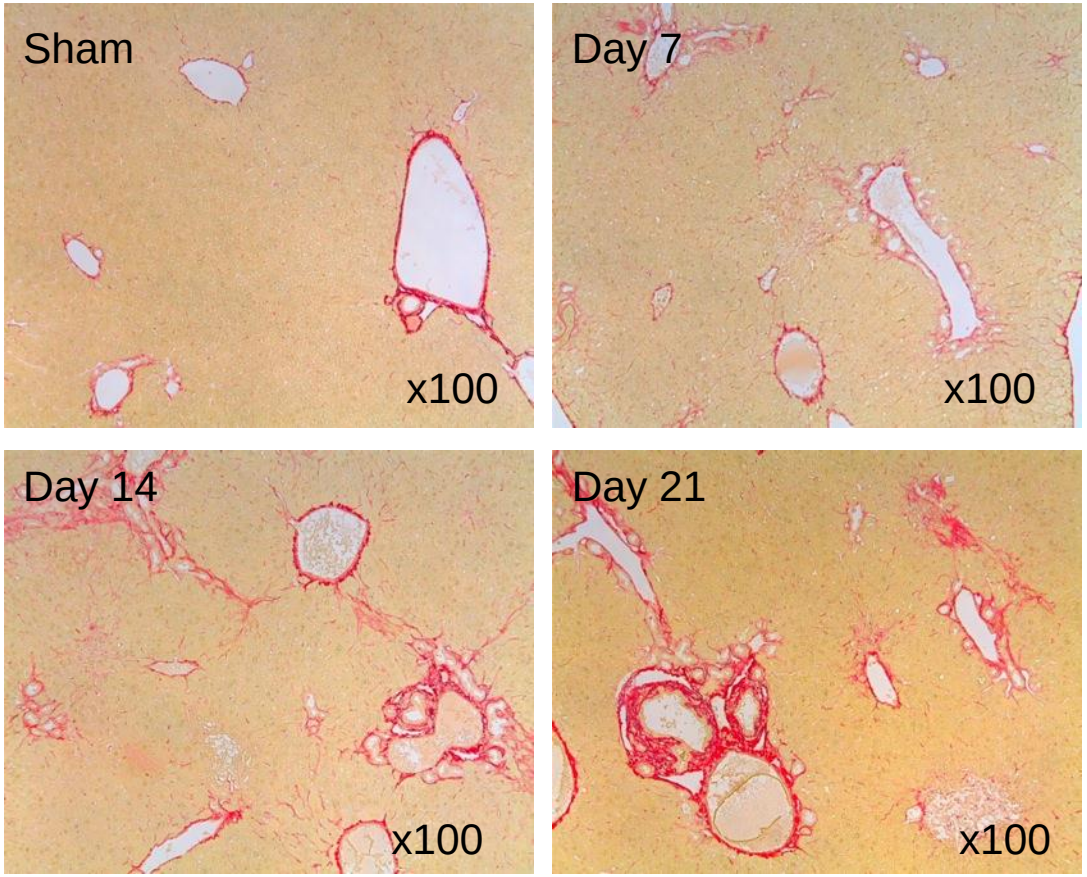
Achievements of BDL model

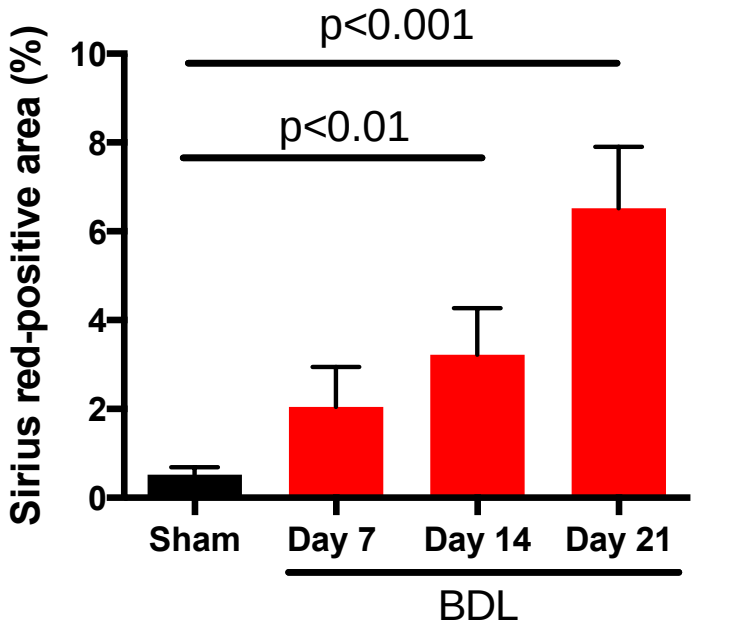
We have a track record of conducting over **30 times** and have evaluated over **70 compounds**. We have experience in drug efficacy evaluation studies using a variety of modalities from small molecules to biologics to meet the needs of our clients.

Pathway	Target
Fibrosis	CB1r
Metabolic	FXR, HMG-CoA reductase
Other	NOX1/NOX4, PPAR-α/PPAR-δ, 5-Lipoxygenase, Chloride Channel, Mast Cell Protease-6

Primary endpoint: Histological analysis of fibrosis

- Representative microphotographs SR-stained liver sections



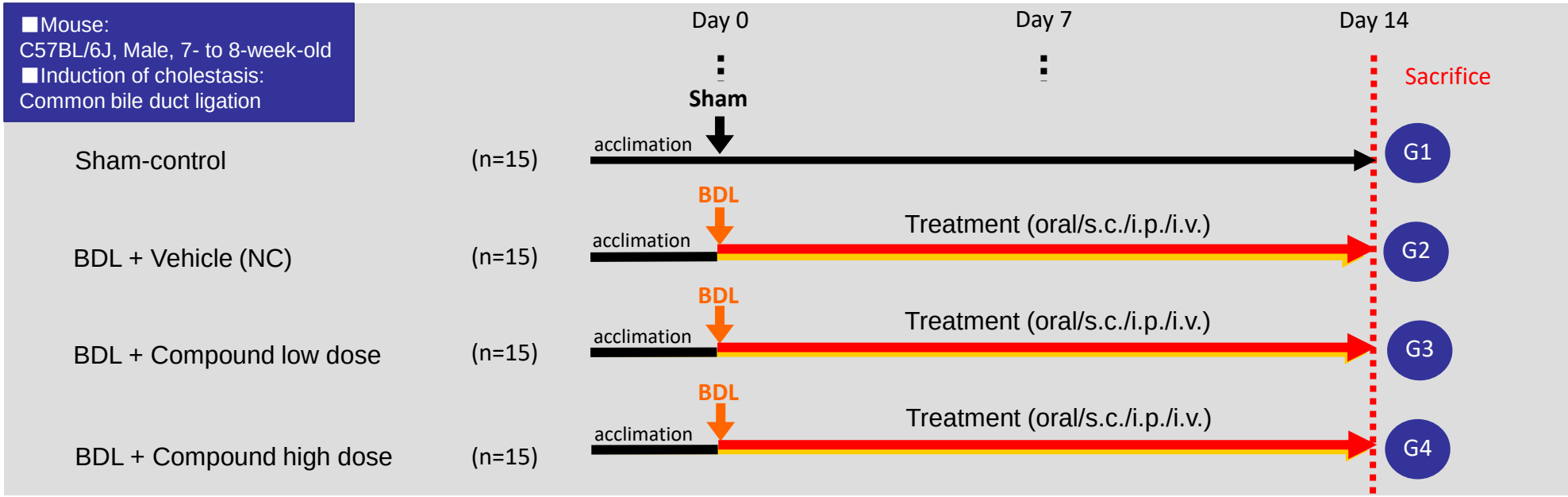


(Mean ± SD, n=3 - 5)

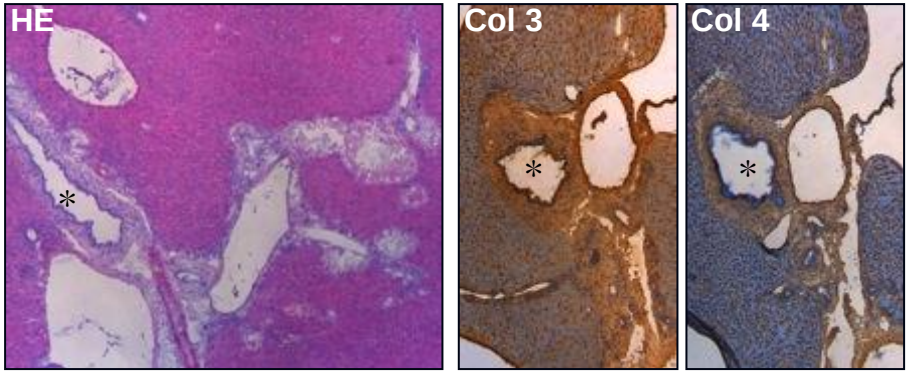
- Collagen deposition and ductal proliferation are visible 7 days after BDL
- Sirius red-positive area is increased about 20-fold by Day 21

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

■Mouse:
C57BL/6J, Male, 7- to 8-week-old
■Induction of cholestasis:
Common bile duct ligation



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