Histopathology and imaging analysis

- SMC’s CRO services in pharmacological R&D-

CONTENTS:
- Company Profile (P2-)
- NASH Services (P4-)
- Basic Services (P12-)

SMC Laboratories, Inc.
www.smclab.co.jp
Facts at a glance

- Founded in October 2006
- A privately-held non-clinical CRO based in Tokyo, Japan; specialized in research on fibrosis and inflammation

CRO services
- **Non-clinical pharmacology**
  - One of the leading CRO in liver research with Proprietary NASH-HCC (STAM™) Model
  - *In vivo* disease models for metabolic disorders, inflammation, fibrosis and tumor
- **Histological imaging services**
  - Histological scoring: NAFLD activity score, fibrosis and inflammation scores etc.
SMC’s CRO services

- **Non-clinical pharmacology study**
  - **High-performance** pharmacology services based on the company’s specialty in fibrosis research
  - **Various lineup** of disease models relating to fibrosis, inflammation, metabolic disorders, and cancer
  - **Strategic** study design proposed by experienced physicians and scientists

- **Histological imaging**
  - **In-house, high quality** analyses; proven skills in Histology
  - **Elaborate and comprehensive** reports by Ph.D. holders
  - **Professional** support for data publication/IND application

### Performance

- **Over 500** clients worldwide
- **Over 90** peer-reviewed papers and presentations
- **10** successful CTA packages

### Region

<table>
<thead>
<tr>
<th>Region</th>
<th>(% of the customers)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Japan</td>
<td></td>
</tr>
<tr>
<td>Europe</td>
<td></td>
</tr>
<tr>
<td>Asia</td>
<td></td>
</tr>
<tr>
<td>North America</td>
<td></td>
</tr>
</tbody>
</table>

### Number of clients

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of clients</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011</td>
<td>100</td>
</tr>
<tr>
<td>2012</td>
<td>150</td>
</tr>
<tr>
<td>2013</td>
<td>200</td>
</tr>
<tr>
<td>2014</td>
<td>250</td>
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<td>2015</td>
<td>300</td>
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<tr>
<td>2016</td>
<td>350</td>
</tr>
<tr>
<td>2017</td>
<td>400</td>
</tr>
<tr>
<td>2018</td>
<td>450</td>
</tr>
</tbody>
</table>
SMC’s outstanding performance in NASH/liver fibrosis research:

- As a leading CRO in NASH, SMC has accumulated know-how by assessing over 500 pharmacology studies and 50,000 slides of NASH and related diseases in mouse, rat and human.
  - judgment of NAS (especially, ballooning), assessment of pathological changes from disease control, discussion of clinical relevance… and more!

Histopathological parameters are important endpoints in nonclinical as well as clinical studies in NASH and liver fibrosis.

For…

- Assessment the grade of disease (NASH, fibrosis) in not only nonclinical pharmacology studies but also clinical studies.
- Development of animal models (including Tg and KO mice) for drug evaluation in the clients’ own laboratory.
- Achievement of high quality report/data package with objective evaluation.
NAS (including ballooning, inflammation, steatosis) is an important parameter to evaluate the drug efficacy in NASH in both human and animal models. In order to translate nonclinical results into clinical practice, it is essential to discriminate “true”- from “pseudo”-ballooning in disease models.
An accurate scoring can evaluate the efficacy of the test substances on each components (steatosis, lobular inflammation, hepatocyte ballooning) of NAS.

### Definition of NAS components

<table>
<thead>
<tr>
<th>Item</th>
<th>score</th>
<th>Extent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steatosis</td>
<td>0</td>
<td>&lt;5%</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>5-33%</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>&gt;33-66%</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>&gt;66%</td>
</tr>
<tr>
<td>Hepatocyte Ballooning</td>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Few balloon cells</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Many cells/prominent ballooning</td>
</tr>
<tr>
<td>Lobular Inflammation</td>
<td>0</td>
<td>No foci</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>&lt;2 foci/200x</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>2-4 foci/200x</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>&gt;4 foci/200x</td>
</tr>
</tbody>
</table>

Tabulation of scoring of steatosis, lobular inflammation, hepatocyte ballooning, and NAFLD activity score in liver sections performed as described in Methods on liver sections obtained from animal livers from the experiment described in Figure 1.

doi:10.1371/journal.pone.0083481.r001

Traber PG et al., PloS One. 2013;8:e83481
The grade of fibrosis (Method)

Steatosis

Steatohepatitis

Fibrosis area: 0.3%

Fibrosis area: 1.0%
The grade of fat (Method)

Threshold setting after extraction

Fat deposition area: 12.9%

Fat deposition area: 4.9%
The grade of inflammation (Method)

Original image

Threshold setting after extraction

Image denoising

NASH-Vehicle

Inflammation area: 8.0%

NASH-Treatment

Inflammation area: 5.6%
Double/ Multiple staining:
- M1(F4/80 + CD16/32) / M2(F4/80 + CD206) ratio.
- Characterization of cytokine-producing cells.
- Identification of target molecule-expressing cells (see the right picture).
- Investigation of proliferative cell types (insulin + BrdU, CD markers + BrdU or Ki-67).
- Cell-cell interaction (inflammatory cells + fibroblast, inflammatory cells + parenchymal cells).
- Optimization of staining method with your developed antibodies and existing antibodies.

- Please ask us!
Assessment of human materials

*Both human and animal samples can be evaluated by the same and standard methods. Useful for discussion of clinical relevance.*

<table>
<thead>
<tr>
<th>Steatosis</th>
<th>Steatohepatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>SR= 1.52%</td>
<td>SR= 5.11%</td>
</tr>
<tr>
<td>SR positive area</td>
<td></td>
</tr>
<tr>
<td>NAS= 2</td>
<td>NAS= 6</td>
</tr>
</tbody>
</table>

Analysis of Collagen proportionate area (CPA) is also available!
Basic services

Processing & Embedding:
• Embedding of human and animal tissues in paraffin (FFPE blocks) from fixed tissues.
• Embedding of human and animal tissues in OCT (frozen OCT embedded tissues) from fixed tissues.
• Instruction of fresh frozen block preparation for frozen sections.

Sectioning:
• Cutting of sections (4-8 µm thick) from paraffin and O.C.T. embedded blocks.
• Preparation of serial thin sections.

Routine staining:
• HE, Sirius red, Masson trichrome, PAS, Oil red, etc.

Immunohistochemistry (IHC):
• Inflammation-related molecules, fibrosis-related molecules etc.
• Functional Immunohistology (Double/multiple staining).
• New antibody staining protocol optimization & validation.

Imaging analysis:
• Area, length, diameter, stained cell count, percentage positive area, shape etc.
• Proliferation, Apoptosis, pathological grading etc.

Interpretation of results:
• Discussion of the histological findings in view of pharmacology.

Reporting:
Fibrosis in various disease models

Providing optimal disease/tissue-specific analytical methods to evaluate the grade of fibrosis in accordance with the types of fibrotic/inflammatory diseases.

### The number of positive cells

- **Model:** DSS-induced colitis model  
  **Organ:** Colon

- **Calculating the α-SMA positive cells per field**

### Positive area

- **Model:** UUO-induced renal fibrosis model  
  **Organ:** Kidney

- **Calculating the Sirius red positive area per field**

### Qualitative score

- **Model:** BLM-induced lung fibrosis model  
  **Organ:** Lung

- Assigning a numerical scale of the amount of fibrotic area (i.e., Ashcroft score)
Evaluation of the grade of inflammation in various tissues in various disease models by using F4/80 as a macrophage markers.
Proliferation and apoptosis in various disease models

Characterization, distribution and quantitative analysis of proliferative/apoptotic cells.

Gut
- Fibroblast + Ki-67

Liver
- TUNEL + Nucleus
- BrdU + Type IV collagen

Insulin positive area, the number of insulin positive cells/proliferating β cells.

The number of insulin positive cells

The number of BrdU+ β cells (after β cell injury by STZ)
Morphometric analysis in kidney injury (Method)

PAS staining → Threshold setting after extraction → PAS-positive area in the tuft (excluding the nuclear region)

Mesangial matrix area = PAS-positive area/tuft area

Okada S et al., Diabetes, 2003;52:2586-93
Target cell counts based on anatomical compartments

Quantitative analysis considering the distribution of cells of interests based on anatomical and functional compartment.

**Ophthalmology:** Retina

**Immunology:** Lymph node

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The number of target cells in GCL

The number of target cells in HEV
Portfolio: non-clinical pharmacology models

- **STAM™: Premium preclinical platform for NASH-HCC**

1. **Pharmacology study**
   - For efficacy evaluation of drug candidates/existing drugs
   - **Histological review** with in-depth knowledge of inflammation and fibrosis

2. **Delivery of STAM™ Mice samples**
   - For target (biomarker) discovery and validation
   - Provided as tissue and/or plasma (serum) samples

- **Conventional disease models**
  - **Fatty liver/NAFLD**: ob/ob model, MCD model
  - **Diabetes mellitus**: nSTZ model
  - **Liver fibrosis**: CCl₄ model, BDL model
  - **Acute liver failure**: CCl₄ model, Concanavalin A model
    - D-gal/LPS model, TAA model
  - **Pulmonary fibrosis**: BLM-induced lung fibrosis model
  - **Skin fibrosis**: BLM-induced skin fibrosis model
  - **Renal diseases**: UUO-induced renal fibrosis model
    - Adriamycin-induced nephropathy model
  - **IBD**: DSS-induced colitis model
  - **COPD**: PPE-induced emphysema model
  - **Alzheimer’s disease**: icv-STZ model
  - **Cancer**: DEN-CCl₄ liver cancer model
    - Xenograft tumor model
Contract Research Laboratory (CRL) capability:

■ **Facility**
  - Accreditation by MEXT*
  - Sponsor audit (QAU)
  - Animal welfare audit by global pharmaceuticals

■ **SPF-grade animal room:**
  - 2080 mice

■ **CRO science team:**
  - 10 full-time researchers
  - 5 visiting scientists (MD, PhD)
  - 3 external pathologists

■ **Equipment:**
  - CT system (*In vivo*)
  - Endoscopy (*In vivo*)
  - Confocal microscopy
  - Dry-chemistry analyzer
  - Real-time PCR
  - Multi-mode microplate reader
  and more…

*MEXT: Ministry of Education, Culture, Sports, Science and Technology*
Publications


41. Experimental Animals, "Analysis of amino acid profiles of blood over time and biomarkers associated with non-alcoholic steatohepatitis in STAM mice" (Exp Anim., DOI: 10.1538/expranim.18-0152, 2019)

40. Frontiers in Genetics, "Gene Expression and DNA Methylation Alterations During Non-alcoholic Steatohepatitis-Associated Liver Carcinogenesis" (Front Genet., May 29:10-486, 2019)


37. NPJ Precision Oncology, "Transcriptomic analysis of hepatocellular carcinoma reveals molecular features of disease progression and tumor immune biology" (NPJ Precis Oncol., DOI: 10.1038/s41698-018-0068-8, 2018)


34. Proc Natl Acad Sci U S A, "Dipeptidyl Peptidase 4 inhibitors Reduce Hepatocellular Carcinoma by Activating Lymphocyte Chemotaxis in Mice" (CMGH, DOI: 10.1016/j.jcmgh.2018.08.008, 2018)

33. Liver Cancer, "Molecular Cancer Research, "Inhibition of the cell death pathway in non-alcoholic steatohepatitis (NASH)-related hepatocarcinogenesis is associated with histone H4 lysine 16 deacetylation" (Molecular Cancer Research, DOI: 10.1158/1541-7786.MCR-17-0109, 2017)


31. Journal of Pharmacology and Experimental Therapeutics, "Distinctly altered gut microbiota in the progression of liver disease" (Onctarget, 7:19355-19366, 2016)

30. The FASEB Journal, "In Vivo Efficacy Study of Milk Thistle Extract (ETHIS-094™) in STAM™ Model of Non-alcoholic Steatohepatitis" (J Immunol Infect Inflam Dis, 1:004, 2016)

29. PLoS One, "Distinctly altered gut microbiota in the progression of liver disease" (Onctarget, 7:19355-19366, 2016)


27. PLoS One, "Distinctly altered gut microbiota in the progression of liver disease" (Onctarget, 7:19355-19366, 2016)

26. Molecular Cancer Research, "Distinctly altered gut microbiota in the progression of liver disease" (Onctarget, 7:19355-19366, 2016)


23. Cell Reports, "Distinctly altered gut microbiota in the progression of liver disease" (Onctarget, 7:19355-19366, 2016)

22. Diabetology & Metabolic Syndrome, "Distinctly altered gut microbiota in the progression of liver disease" (Onctarget, 7:19355-19366, 2016)

21. Journal of Immunology, Infection & Inflammatory Diseases, "Distinctly altered gut microbiota in the progression of liver disease" (Onctarget, 7:19355-19366, 2016)


18. Journal of Immunology, Infection & Inflammatory Diseases, "Distinctly altered gut microbiota in the progression of liver disease" (Onctarget, 7:19355-19366, 2016)

17. PLoS One, "Distinctly altered gut microbiota in the progression of liver disease" (Onctarget, 7:19355-19366, 2016)

16. Cell Reports, "Distinctly altered gut microbiota in the progression of liver disease" (Onctarget, 7:19355-19366, 2016)

15. International Journal of Gastroenterology, "Distinctly altered gut microbiota in the progression of liver disease" (Onctarget, 7:19355-19366, 2016)


13. Cancer Research, "Distinctly altered gut microbiota in the progression of liver disease" (Onctarget, 7:19355-19366, 2016)

12. Drug R D, "Distinctly altered gut microbiota in the progression of liver disease" (Onctarget, 7:19355-19366, 2016)


7. PLoS One, "Distinctly altered gut microbiota in the progression of liver disease" (Onctarget, 7:19355-19366, 2016)


5. PLoS One, "Distinctly altered gut microbiota in the progression of liver disease" (Onctarget, 7:19355-19366, 2016)


2. PLoS One, "Distinctly altered gut microbiota in the progression of liver disease" (Onctarget, 7:19355-19366, 2016)

1. PLoS One, "Distinctly altered gut microbiota in the progression of liver disease" (Onctarget, 7:19355-19366, 2016)
Publications and Presentations

■ Publications (continued)

10. Cancer Science, "Silencing of microRNA-122 is an early event during hepatocarcinogenesis from non-alcoholic steatohepatitis" (Cancer Sci, 105:1254-60, 2014)


7. Medical Molecular Morphology, "Linagliptin alleviates hepatic steatosis and inflammation in a mouse model of non-alcoholic steatohepatitis" (Med Mol Morph, 47:137-149)


2. Hepatology, "Hydrogen-rich water prevents progression of non-alcoholic steatohepatitis and accompanying hepatocarcinogenesis in mice" (Hepatology, 56:912-921, 2012)


■ Presentations

73. DDW 2019, "Change of Gut Microbiome after Treatment with the Traditional Japanese Medicine Daisaikoto is Associated with Improved Liver Steatosis in a Non-alcoholic Fatty Liver Mouse Model" TSUMURA & Co.

72. DDW 2019, "Influence of the O-GlcNAc Modification in Hepatic Carcinogenesis by Non-alcoholic Fatty Liver Disease" Osaka Medical College

71. EASL the International Liver Congress™ 2018, "LXR inverse agonists reduce steatosis and fibrosis in the STAM mouse model but also improve insulin sensitivity in a high fat diet mouse clamp study" Phenex Pharmaceuticals AG

70. 3rd Annual World Preclinical Conference Europe 2018, "LXR Inverse Agonists for the Treatment of NASH" Phenex Pharmaceuticals AG

69. 3rd Annual World Preclinical Congress Europe 2018, "MTBL0036, a Promising, New Anti-NASH and Antifibrotic Candidate: MTBL0036 showed a decrease in NAFLD Activity score in the STAM model" Metabolys, Inc.

68. AASLD 2018, "AXA1125, a Novel Composition of Amino Acids Reprograms the Multifactorial Pathophysiology in NAFLD" Acelle Health Inc.

67. AASLD 2018, "Treatment of Hepatocellular Carcinoma Using 2-Deoxy-D-Glucose Encapsulated in PLGA Nanoparticles in Mice" Kawasaki Medical School

66. AASLD 2018, “Dipeptidyl Peptidase 4 Inhibitors Reduce the Progression of Hepatocellular Carcinoma By Activating T Cell and Natural Killer Cell Chemotaxis in Mice” Kawasaki Medical School

65. AASLD 2018, “Effects of a DPP4 Inhibitor on Progression of Nash-Related Hepatoma and DNA Synthesis Pathway Via p62/Keap1/Nrf2 in a Mouse Model: A Metabolicomic Analysis” Kurume University School of Medicine

64. AASLD 2018, “Gemcabene Regulates Hepatic Genes Associated with Inflammation and Fibrosis with Impact on Non-Alcoholic Fatty Liver Disease” Gempshire Therapeutics Inc.

63. AASLD 2018, “CM101, a Novel CCL24 Blocking Antibody, Suppresses Hepatic Injury and Fibrosis in Experimental Models of NASH and Liver Fibrosis” ChemomAb Ltd.

62. AASLD 2018, “Unexpected Antidiabetic Effects Combined with Antifibrotic Activities of LXR Inverse Agonists in Mouse Models of NAFLD/NASH” Phenex Pharmaceuticals AG

61. The 78th Scientific Sessions ADA, 2018, “Canagliflozin, an SGLT2 Inhibitor, Prevents Development of Hepatocellular Carcinoma (HCC) from Nonalcoholic Steatohepatitis (NASH) in a Mouse Model of NASH-HCC Under Diabetic State” Dokkyo Medical University

60. The 78th Scientific Sessions ADA, 2018, “Combination of SGLT2 Inhibitor and Novel Selective PPARα Modulator, Tofagliflozin (Tofo) and Pemafibrate (Pema), Improves Survival Rate in STAM Mice as a Diabetic NASH Model” Kowa Company Ltd.

59. EASL the International Liver Congress™ 2018, “Interfering with local fibrotic platelet activation significantly inhibits fibrosis in multiple animal models: suggestions of the importance of the platelet-wound healing axis for fibrosis” Symic Bio, Inc.

58. EASL the International Liver Congress™ 2018, “BMS-986036, a PEGylated fibroblast growth factor 21 analogue, reduces fibrosis and PRO-C3 in a mouse model of non-alcoholic steatohepatitis” Bristol-Myers Squibb Company

57. EASL the International Liver Congress™ 2018, “LJN452 (tropifexor) attenuates steatohepatitis, inflammation, and fibrosis in dietary mouse models of nonalcoholic steatohepatitis” Genomics Institute of the Novartis Research Foundation

56. EASL the International Liver Congress™ 2018, “Clinical-grade human liver mesenchymal stem cells reduce NAS score and fibrosis progression in advanced stage NASH pre-clinical model through immunomodulation” Promethera Biosciences LLC

55. First EASL NAFLD Summit 2017, “Dual CCR2/5 antagonist decreases hepatic inflammation in acute liver injury and NASH metabolic animal models” Pfizer Inc.

54. First EASL NAFLD Summit 2017, “AXA1125, a novel defined amino acid composition (DAAC), improves NAFLD activity score (NAS) and reduces fibrosis in two rodent models of nonalcoholic steatohepatitis (NASH)” Acelle Health, Inc.

52. AASLD 2017, "DP4 Inhibitor Suppressed Progression of NASH-related Hepatocellular Carcinoma with Inhibition of Metabolic Reprogramming in p62-Keap 1-Nrf2-pentose Phosphate Pathway in a Mouse Model: A Metabolomic Analysis" Kurume University School of Medicine

51. AASLD 2017, "CB4209 and CB4211 Reduce the NAFLD Activity Score in the STAM Model of NASH, Reduce Triglyceride Levels, and Induce Selective Fat Mass Loss in DIO Mice" CohBar, Inc.

50. AASLD 2017, "Combination Treatment of LJN452 and Cenicriviroc Shows Additive Effects in a Diet-Induced NASH Model" Genomics Institute of the Novartis Research Foundation/Allergan plc/Novartis Institutes for BioMedical Research, Inc.

49. AASLD 2017, "Gemcabene Attenuates the NAFLD Activity and Fibrosis Scores, and Downregulates Hepatic Inflammatory Genes in the STAM™ Murine Model of NASH-HCC“ Gemphire Therapeutics Inc.

48. DDW 2017, "A HMG-CoA Reductase Inhibitor, Rosuvastatin, as a Potential Preventive Drug for The Development of Hepatocellular Carcinoma Associated With Non-alcoholic Fatty Liver Disease in Mice" Osaka Medical College

47. EASL the International Liver Congress™ 2017, "Anti-fibrotic effect of NV556, a sangfiehrin-based cyclophilin inhibitor, in a preclinical model of non-alcoholic steatohepatitis" Neuro Vive Pharmaceutical AB

46. AACC 2017, "Inhibition of gene expression during non-alcoholic steatohepatitis (NASH)-related hepatocarcinogenesis is mediated by histone H4 lysine 16 deacetylation" FDA-National Center for Toxicological Research.

45. AACC 2017, "Alterations in the chromatin accessibility in nonalcoholic steatohepatitis-associated hepatocellular carcinoma" FDA-National Center for Toxicological Research

44. AACC 2017, "Role of miRNAome deregulation in the pathogenesis of non-alcoholic steatohepatitis (NASH)-derived hepatocellular carcinoma" FDA-National Center for Toxicological Research


42. AASLD 2017, Emerging Trends Conference: Emerging Trends in Non-Alcoholic Fatty Liver Disease, "DUR-928, An Endogenous Regulatory Molecule, Exhibits Anti-Inflammatory and Antifibrotic Activity in a Mouse Model of NASH" DIRECT Corporation

41. AASLD 2016, "A Phase 2 study of BMS-986036 (Pegylated FG21) in Obese Adults with Type 2 Diabetes and a High Prevalence of Fatty Liver" Bristol-Myers Squibb Company

40. AASLD 2016, "Effects of BMS-986036 (pegylated fibroblast growth factor 21) on hepatic steatosis and fibrosis in a mouse model of non-alcoholic steatohepatitis” Bristol-Myers Squibb Company.

39. DDW 2016, "Inhibition of the Ileal Bile Acid Transporter (IBAT) by A4250 Reduces Hepatic Damage in a Mouse Model of Non-Alcoholic Steatohepatitis (NASH)" Albireo AB

38. EASL the International Liver Congress™ 2016, "DP4 Inhibitor Suppresses Steatohepatitis and HCC Progression with Glucose Re-Programming in a Mouse Model of NASH" Kurume University School of Medicine

37. HEP DART 2015, "The Cyclophilin Inhibitor, CPI-431-32, is a Hepatitis B Oral Drug Candidate with Antiviral and Antifibrotic Activities" Ciclophilin Pharmaceuticals Inc.

36. WDC 2015, "Empagliflozin (an SGLT2 inhibitor), alone or in combination with linagliptin (a DPP-4 inhibitor), prevents steatohepatitis in a novel mouse model of non-alcoholic steatohepatitis and diabetes" Dokkyo University

35. AASLD 2015, "Anti-Fibrotic Effect of Autotaxin and LPA1R Antagonists in a Rodent Model of NASH” Bristol-Myers Squibb Company

34. AASLD 2015, "Sitagliptin, a Dipeptidyl Peptidase 4 inhibitor, Suppressed Tumor Progression with Down-regulation of Nrf Nuclear Expression in a Mouse Model of Non-alcoholic Steatohepatitis-related Hepatocellular Carcinoma” Kurume University School of Medicine

33. AASLD 2015, "Reduction of Hepatic 27-Hydroxycholesterol in Steatohepatitis Model Mice with Insulin Resistance" Tokyo Medical University Ibaraki Medical Center

32. AASLD 2015, "Disturbance of regulatory T cells, MDSCs and NK cells is involved in NASH and mouse model of NASH” Tohoku University Hospital.

31. AASLD 2015, "Mechanism of Action of the Anti-NASH effects of Solithromycin in a Predictive NASH HCC Mouse Model” Cempra Pharmaceuticals, Inc.

30. DDW 2015, "Effects of Sitagliptin, a Dipeptidyl Peptidase 4 Inhibitor, on Tumor Progression and p62/SQSTM1 Subcellular Localization in a Mouse Model of Non-Alcoholic Steatohepatitis-Related Hepatocellular Carcinoma” Kurume University

29. Keystone Symposia 2015, "DGAT2 Inhibition Prevents NAFLD and Fibrosis in the STAM Mouse Model of NASH” Pfizer Inc.


27. AASLD 2014, "L-carnitine prevents progression of non-alcoholic steatohepatitis in a mouse model with upregulation of mitochondrial pathway" Department of Gastroenterology and Hepatology, Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences

26. AASLD 2014, "MN-001 (tipelukast), a novel, orally bioavailable drug, reduces fibrosis and inflammation and down-regulates TIMP-1, collagen Type 1 and LOXL2 mRNA overexpression in an advanced NASH (nonalcoholic steatohepatitis) model” MediciNova, Inc.

25. ICLAF 2014, "MN-001 (tipelukast), a nonselective phosphodiesterase, 5-lipoxygenase, leukotriene, phospholipase C and thromboxane A2 inhibitor, demonstrates anti-fibrotic effects in the bleomycin-induced idiopathic pulmonary fibrosis mouse model” MediciNova, Inc.

24. ADA 2014, "Liraglutide prevents steatohepatitis, liver fibrosis, and accompanying carcinogenesis in a diabetes and nonalcoholic steatohepatitis mouse model treated with STZ-HFD” Saga University

23. ATS 2014, "Solithromycin Reduces Inflammation In Mice Caused By Bleomycin-Induced Lung Injury” Cempra, Inc.


21. AACC 2014, "Clinicopathological characterization of non-alcoholic Steatohepatitis (NASH)-derived Hepatocellular carcinoma (HCC) as a patient stratification model in mice” The Jikei University School of Medicine
Presentations (continued)

5. EASL The International Liver Congress™ 2012 - 47th Annual Meeting of the European Association for the Study of the Liver, “FXR agonists prevent steatosis, hepatocyte death and progression of NASH towards HCC in a hypoinsulinaemic mouse model of progressive liver disease” Phenex Pharmaceuticals AG

4. AASLD 2011, “The Dipeptidyl Peptidase-4 Inhibitor Linagliptin is an Effective Therapeutic for Metabolic Liver Disease in Several Rodent Models of Non-Alcoholic Fatty Liver Disease (NAFLD) and Non-Alcoholic Steatohepatitis (NASH)” Boehringer Ingelheim GmbH & Co. KG

3. EASL Special Conference - Liver Transplantation 2011, “Improvement of steatosis, inflammation, and fibrosis in a mouse model of steatohepatitis following treatment with galectin inhibitor” Galectin Therapeutics Inc.

2. EASL The International Liver Congress™ 2011 - 46th Annual Meeting of the European Association for the Study of the Liver, “Novel FXR agonists with potent lipid lowering, insulin sensitising, anti-inflammatory and anti-fibrotisation effects in mouse models of metabolic syndrome and NASH” Phenex Pharmaceuticals AG


Patents

- International publication No.: WO2011/013247 Title of the invention: “Steatohepatitis-Liver Cancer Model Animal”

List of presentations in domestic meeting is available only in Japanese version.
Dendritic cells efflux from the liver through lymph

Distribution of proliferating B cells during the second challenge of immune responses

Clustering between dendritic cells and proliferating T cells in the liver

Fat-laden Kupffer cells in NASH liver

Clustering between HSCs and dividing hepatocytes