

藤嘉朗：メタボロミクスを用いた肝臓性リン脂質症の血中バイオマーカー探索. 第34回日本臨床薬理学会学術総会 (2013.12 (東京))

8) Saito K, Maekawa K, Pappan KL, Urata M, Ishikawa M, Kumagai Y, Saito Y: The difference in the hydrophilic metabolite profiles between plasma and serum in human subject. 28th JSSX meeting 2013.10 (Tokyo)

9) Saito K, Maekawa K, Pappan KL, Urata M, Ishikawa M, Kumagai Y, Saito Y: The difference in the metabolite profiles between plasma and serum, ages or sexes, and their inter-individual variations in human subjects. 10th international ISSX meeting 2013.10 (Toronto)

10) Ishikawa M, Maekawa K, Senoo Y, Tajima Y, Saito K, Urata M, Murayama M, Kumaga Y, Saito Y: Lipidomic profiles in blood from fasted healthy adults vary between plasma and serum and by subject's genders and ages. 10th international ISSX meeting 2013.10 (Toronto)

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12) 石川 将己, 前川 京子, 齊藤 公亮, 浦田 政世, 田島 陽子, 村山 真由子, 妹尾 勇弥, 熊谷 雄治, 斎藤 嘉朗: ラット血清中の内因性代謝物レベルの雌雄差に関する網羅的検討. 第34回日本薬学会年会 2014.3 (熊本)

13) 前川 京子, 齊藤 公亮, 山田 弘, 斎藤 嘉朗: 動物モデルを用いた医薬品化合物によるリン脂質症の脂質メタボローム解析. 第34回日本薬学会年会 2014.3 (熊本)

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Kumagai Y, Maekawa K, Saito Y.: Comparison of plasma lipidomic profile of humans with preclinical animals. 19th North American ISSX and 29th JSSX Joint Meeting (2014.10, San Francisco, CA, USA).

15) Maekawa K, Saito K, Pappan K, Ishikawa M, Urata M, Tajima Y, Murayama M, Kumagai Y, Saito Y.: Impact of gender, age, fed/fasted state of rats on their serum hydrophilic metabolites. 19th North American ISSX and 29th JSSX Joint Meeting (2014.10, San Francisco, CA, USA).

16) Saito Y, Saito K, Ishikawa M, Urata M, Tajima Y, Inoue M, Kumagai Y, Pappan K, Maekawa K.: Metabolomic profiles in rat blood vary between genders, ages and fasting conditions, and their qualitative comparisons with human samples. 2014 AAPS Annual Meeting and Exposition (2014.11 San Diego, CA, USA).

17) Maekawa K, Saito K, Ishikawa M, Minamino M, Kumagai Y, Saito Y.: Metabolomic biomarker exploration highlights issues of species specificity. KSCPT-JSCPT Joint symposium (2014.11, Busan, Korea).

18) 斎藤嘉朗, 齊藤公亮, 児玉進, 熊谷雄治, 前川京子: ヒト試料を用いたバイオマーカー研究のためのレギュラトリーサイエンス. 第35回日本臨床薬理学会学術総会(2014.12, 愛媛)

H. 知的財産権の出願・登録状況:

1. 特許出願
なし

2. 実用新案登録
なし

3. その他
特になし

表1 血漿メタボローム解析に用いたラット検体の種類と検体情報

| Group | sex | age | weight | Number of samples | Fastin g | Sampling time |
|-------|--------|----------|--------------------------------|-------------------|----------|---------------|
| 1 | Male | 10 weeks | 349.22±20.65 | 11 | 16 hr | 10:00 AM |
| 2 | Female | 10 weeks | 227.72±14.96 ^{***} | 11 | 16 hr | 10:00 AM |
| 3 | Male | 30 weeks | 577.76±37.27 ^{†††} | 13 | 16 hr | 10:00 AM |
| 4 | Female | 30 weeks | 305.42±24.18 ^{***†††} | 12 | 16 hr | 10:00 AM |
| 5 | Male | 10 weeks | 405.9±26.98 ^{§§§} | 11 | No | 10:00 AM |
| 6 | Male | 10 weeks | 361.64±32.93 | 11 | 22 hr | 10:00 AM |
| 7 | Male | 10 weeks | 347.57±13.37 | 11 | 22 hr | 4:00 PM |

***, p < 0.005 for the comparison between male and female rats of same aged groups (Group 1 vs. Group 2, Group 3 vs. Group 4).

†††, p < 0.005 for the comparison between young and old rats of same sex groups (Group 1 vs. Group 3, Group 2 vs. Group 4).

§§§, p < 0.005 for the comparison between fasting and nonfasting rats of same age and sex groups (Group 1 vs. Group 5).

表2-A 血漿・血清メタボロームに用いた白人健常ボランティアの情報と検体の種類

| Groups | [CMY] Young male | [CFY] Young female | [CMO] Elderly male | [CFO] Elderly female | Statistical significance |
|-----------------------------------|------------------------|-------------------------|------------------------|-------------------------|---|
| Gender | Male | Female | Male | Female | |
| Number | 15 | 15 | 15 | 15 | |
| Median age [range] | 29 [25-33] | 28 [25-34] | 59 [55-64] | 59 [55-63] | |
| Median Weight (Kg) [range] | 78 [52.2-113.9] | 93.4 [59.9-147.4] | 75.6 [63.5-116.1] | 90.7 [62.6-114.3] | [1] vs. [2] (N.S.), [3] vs. [4] (N.S.), [1] vs. [3] (N.S.), [2] vs. [4] (N.S.) |
| Median height (cm) [range] | 172.7 [154.9-185.4] | 162.6 [149.9- 182.9] | 177.8 [165.1-190.5] | 162.6 [152.4- 175.3] | [1] vs. [2] (p=0.017), [3] vs. [4] (p=0.0001), [1] vs. [3] (p=0.032), [2] vs. [4] (N.S.) |
| Median BMI [range] | 26.2 [18.0-36.6] | 35.4 [24.9- 49.7] | 24.5 [19.5-34.9] | 32.7 [26.1- 43.3] | [1] vs. [2] (p=0.042), [3] vs. [4] (p=0.0008), [1] vs. [3] (N.S.), [2] vs. [4] (N.S.) |
| matrices | plasma/serum | plasma/serum | plasma/serum | plasma/serum | |
| freeze-thaw (plasma and serum) | 2 and 10 times | 2 times | 2 times | 2 times | |

N.S: not significant

表2-B 血漿メタボロームに用いた日本人健常ボランティアの情報と検体の種類

| Groups | [JMY] Japanese Young male | [JFY] Japanese Young female | [JMO] Japanese Elderly male | [JFO] Japanese Elderly female | Statistical significance |
|-------------------------------|---------------------------------|-----------------------------------|-----------------------------------|-------------------------------------|---|
| Gender | Male | Female | Male | Female | |
| Number | 15 | 15 | 15 | 15 | |
| Median age [range] | 32 [25-35] | 32 [25-35] | 60 [55-64] | 60 [55-65] | |
| Median Weight (Kg) [range] | 64 [53-72] | 54 [44-73] | 65 [53-83] | 51 [43-61] | [JMY] vs. [JFY] (p=0.0054), [JMO] vs. [JFO] (p<0.0001), [JMY] vs. [JMO] (N.S.), [JFY] vs. [JFO] (N.S.) |
| Median height (cm) [range] | 171 [165-180] | 162 [151- 175] | 167 [161-182] | 156 [143- 161] | [JMY] vs. [JFY] (p=0.0001), [JMO] vs. [JFO] (p<0.0001), [JMY] vs. [JMO] (N.S.), [JFY] vs. [JFO] (p=0.0039) |
| Median BMI [range] | 22 [19-24] | 20 [19- 25] | 23 [20-25] | 21 [18- 25] | [JMY] vs. [JFY] (N.S.), [JMO] vs. [JFO] (p=0.0265), [JMY] vs. [JMO] (p=0.0161), [JFY] vs. [JFO] (N.S.) |
| matrices | plasma | plasma | plasma | plasma | |

N.S: not significant

表2-C 本研究に用いた若年男性ボランティア(日本人、黒人、白人)の情報と検体の種類

| Groups | [JMY] Japanese Young male | [AMY] African Young male | [CMY] Caucasian Young male | Statistical significance |
|-------------------------------|---------------------------------|--------------------------------|----------------------------------|---|
| Gender | Male | Male | Male | |
| Number | 15 | 15 | 15 | |
| Median age [range] | 32 [25-35] | 29 [26-33] | 29 [25-33] | |
| Median Weight (Kg) [range] | 64 [53-72] | 74 [54-130] | 78 [52.2-113.9] | [JMY] vs. [AMY] (p=0.0037), [JMY] vs. [CMY] (p=0.0225), [AMY] vs. [CMY] (N.S.) |
| Median height (cm) [range] | 171 [165-180] | 180 [165- 196] | 172.7 [154.9-185.4] | [JMY] vs. [AMY] (p=0.0037), [JMY] vs. [CMY] (p=0.0062), [AMY] vs. [CMY] (p=0.0379) |
| Median BMI [range] | 22 [19-24] | 22 [18- 34] | 26.2 [18.0-36.6] | [JMY] vs. [AMY] (N.S.), [JMY] vs. [CMY] (p=0.0062), [AMY] vs. [CMY] (N.S.) |
| matrices | plasma | plasma | plasma | |

N.S: not significant

表3 検出された脂質代謝物のクラスと主な分子種

| Lipid types | Detected ion mode | Lipid classes | Number of molecules detected ¹⁾ | | |
|---|-------------------|---|--|-------------------|------------------|
| | | | Rat | Human (Caucasian) | Human (Japanese) |
| Glycerophospholipid | Negative | lysophosphatidylcholine (LPC) | 9 | 9 | 6 |
| | | lysophosphatidylethanolamine (LPE) | 1 | 2 | 0 |
| | | phosphatidylcholine (PC) | 40 | 34 | 35 |
| | | ether-type PC (ePC) | 4 | 20 | 19 |
| | | phosphatidylethanolamine (PE) | 4 | 9 | 7 |
| | | ether-type PE (ePE) | 3 | 9 | 16 |
| | | phosphatidylinositol (PI) | 7 | 8 | 9 |
| Sphingolipid | Negative | sphingomyelin (SM) | 14 | 22 | 26 |
| | | ceramide (Cer) | 5 | 7 | 4 |
| | | hexosylceramide (HexCer) | 1 | 8 | 6 |
| Neutral lipid (Simple lipid) | Positive | cholesterol/cholesterolester (Ch/ChE) | 26 | 13 | ND |
| | | diacylglycerol (DG) | 10 | 7 | ND |
| | | triacylglycerol (TG) | 101 | 79 | ND |
| | | coenzyme Q (CoQ) | 1 | 1 | ND |
| Polyunsaturated fatty acids (PUFAs) and their metabolites | Negative | arachidonic acid (AA) and its metabolites | 18 | 13 | 22 |
| | | eicosapentaenoic acid (EPA) and its metabolites | 8 | 4 | 8 |
| | | docosahexaenoic acid (DHA) and its metabolites | 10 | 6 | 8 |
| total | | | 262 | 251 | 166 |

ND, not determined yet

表4 ラット血漿中の内在性代謝物濃度に及ぼす試料採取条件(雌雄差・週齢差・食餌状態及び採血時間)の影響

| Statistical Comparisons | | | | | | | |
|--|--------------------------|---------------------------|-------------------------|------------------------|---------------------------|---------------------------|--|
| Welch's Two-Sample t-Test | Gender Comparison: | | Age comparison: | | Fasting status | Time of sample collection | |
| | 16h fast, AM collection | | 16h fast, AM collection | | 10wk Males | 22h PM (G7) | |
| | F 10wk (G2) | F 30wk (G4) | M 30wk (G3) | F 30wk (G4) | NF AM (G5) | 22h AM (G6) | |
| | M 10wk (G1) | M 30wk (G3) | M 10wk (G1) | F 10wk (G2) | 16h AM (G1) | | |
| Total biochemicals (262 in total) <i>p</i> < 0.05 | 110 (42%) | 142 (54%) | 76 (29%) | 101 (39%) | 183 (70%) | 17 (6.5%) | |
| Biochemicals (Increase Decrease) | 59 51 (23%) (19%) | 111 31 (42%) (12%) | 15 61 (6%) (23%) | 98 3 (37%) (1%) | 148 35 (56%) (13%) | 6 11 (2%) (4%) | |
| Phospholipids (68 in total) | 28 8 | 46 1 | 3 21 | 18 0 | 44 2 | 0 6 | |
| Sphingolipids (20 in total) | 13 4 | 14 2 | 1 6 | 8 0 | 3 4 | 0 1 | |
| Neutral lipids (138 in total) | 15 38 | 30 27 | 11 16 | 71 1 | 96 13 | 6 4 | |
| PUFAs and metabolites (36 in total) | 3 1 | 21 1 | 0 18 | 1 2 | 5 16 | 0 0 | |
| Common Biochemicals (Increase Decrease) | 41 26 (16%) (10%) | | 14 2 (5%) (1%) | | | | |

表5 白人血液中の内在性代謝物濃度に及ぼす試料採取条件(血漿・血清差、男女差、年齢差)及び試料保管条件(凍結融解の回数)の影響

| Statistical Comparisons | | | | | | | |
|--|------------------------|------------------------|------------------------|------------------------|----------------------|------------------------|-------------------------|
| Wilcoxon signed-rank test (matrix, freeze thaw) Mann-Whitney U-test (gender, age) | Matrix comparison: | | Gender Comparison: | | Age comparison: | | Freeze Thaw |
| | 14h fast | | 14h fast, plasma | | 14h fast, plasma | | CMY plasma |
| | serum (CMY) plasma | serum (CFY) plasma | CFY | CFQ | CMQ | CFQ | 10 times 2 times |
| Total biochemicals (251 in total) <i>p</i> < 0.05 | 34 (14%) | 82 (33%) | 16 (6%) | 61 (24%) | 8 (3%) | 81 (32%) | 201 (80%) |
| Biochemicals (Increase Decrease) | 23 11 (9%) (4%) | 73 9 (29%) (4%) | 10 6 (4%) (2%) | 56 5 (22%) (2%) | 8 0 (3%) (0%) | 78 3 (31%) (1%) | 7 194 (3%) (77%) |
| Phospholipids (91 in total) | 7 3 | 11 1 | 0 4 | 25 0 | 1 0 | 29 0 | 0 85 |
| Sphingolipids (37 in total) | 0 0 | 3 1 | 10 0 | 21 0 | 0 0 | 4 0 | 0 27 |
| Neutral lipids (100 in total) | 6 2 | 50 2 | 0 1 | 10 0 | 4 0 | 45 0 | 7 59 |
| PUFAs and metabolites (23 in total) | 10 6 | 9 5 | 0 1 | 0 5 | 3 0 | 0 3 | 0 23 |
| Common Biochemicals (Increase Decrease) | 22 6 (9%) (2%) | | 9 1 (4%) (0.4%) | | 4 0 (2%) (0%) | | |

表6 日本人血液中の内在性代謝物濃度に及ぼす試料採取条件(男女差、年齢差)及び人種差の影響

| Statistical Comparisons | | | | | | |
|--|-------------------------|------------------------|------------------------|------------------------|--------------------------|--------------------------|
| Mann whitney t-Test | Gender Comparison: | | Age comparison: | | Ethnic comparison: | |
| | 14h fast, plasma | | 14h fast, plasma | | 14h fast, plasma | |
| | JFY | JFQ | JMQ | JFQ | CMY | AMY |
| | JMY | JMO | JMY | JFY | JMY | JMY |
| Total biochemicals <i>p</i> ≤ 0.05 | 10 (6%) | 21 (13%) | 49 (30%) | 39 (23%) | 45 (35.2%) | 60 (46.9%) |
| Biochemicals (Increase Decrease) | 10 0 (6.0%) (0%) | 18 3 (11%) (2%) | 46 3 (28%) (2%) | 32 7 (19%) (4%) | 15 30 (12%) (23%) | 39 21 (30%) (16%) |
| Phospholipids (92 in total) | 9 0 | 7 2 | 32 3 | 18 6 | 15 22 | 38 16 |
| Sphingolipids (36 in total) | 1 0 | 11 0 | 5 0 | 6 1 | 0 8 | 1 5 |
| Neutral lipids | ND | ND | ND | ND | ND | ND |
| PUFAs and metabolites (38 in total) | 0 0 | 0 1 | 9 0 | 8 0 | ND | ND |
| Common Biochemicals (Increase Decrease) | 1 0 (0.8%) (0%) | | 20 3 (10%) (2%) | | 15 19 (12%) (15%) | |

ND, not determined yet

表7 薬物性肝障害患者12名の内訳と臨床検査値等

| 臨床病型 | 人数 | 性別 (男/女) | 年齢 中央値(範囲) | ALT (U/L) 中央値(範囲) | ALP (U/L) 中央値(範囲) | T.bil (mg/dL) 中央値(範囲) | 2004DDW-Jスコア 中央値(範囲) |
|--------|----|-------------|---------------|----------------------|----------------------|--------------------------|-------------------------|
| 肝細胞障害型 | 9 | (4, 5) | 63 (33-80) | 1362 (80-4093) | 360 (219-1398) | 1.38 (0.5-6.2) | 7 (4-10) |
| 混合型 | 2 | (0, 2) | 50 (29-70) | 341 (290-391) | 1225 (1057-1398) | 2.57 (1.28-3.85) | 6 (5-7) |
| 不明 | 1 | (0, 1) | 77 | U.N | U.N | U.N | U.N |

図1 ラット及び白人血漿中において性差を認めた代謝物の比較

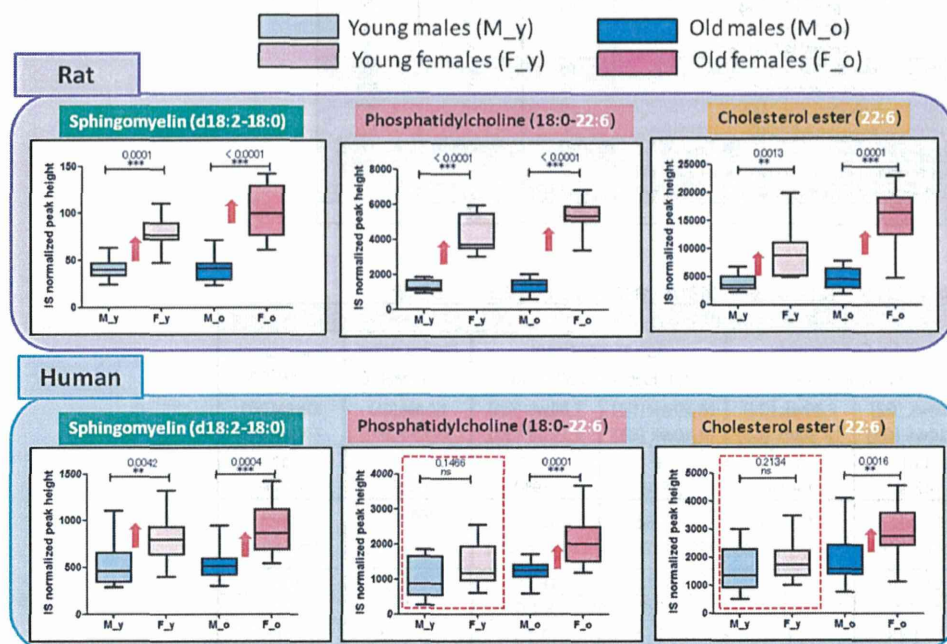


図2 ラット及び白人血漿中において年齢差を認めた代謝物の比較

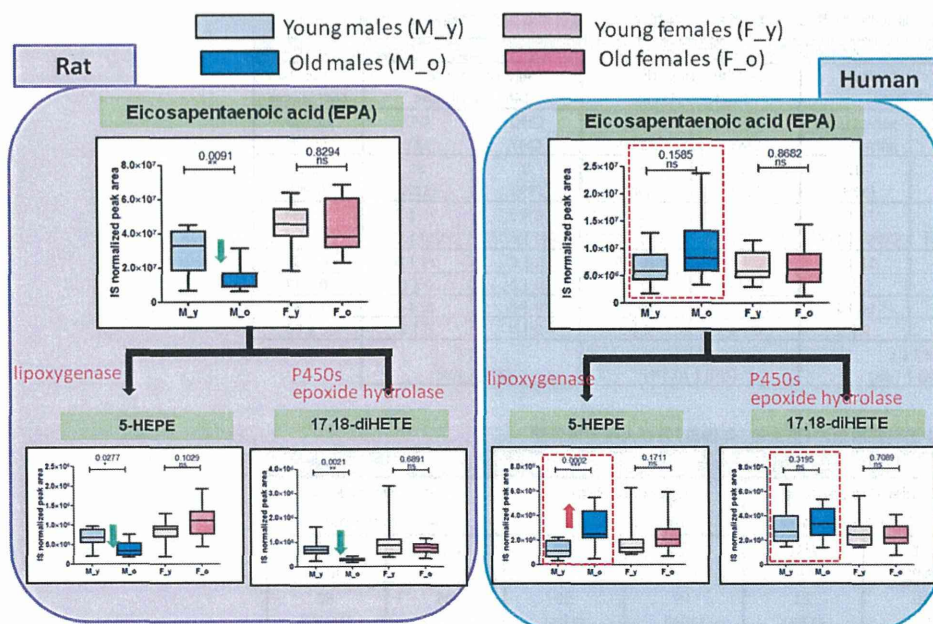
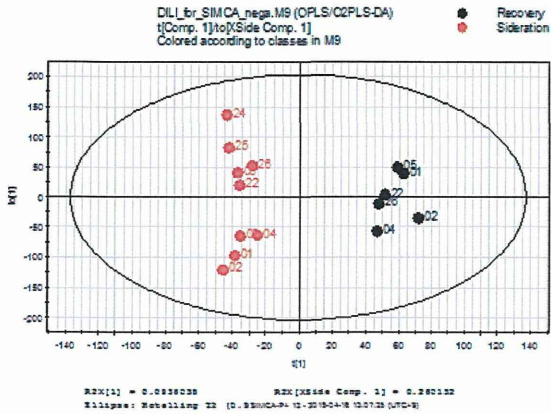


図3 薬物性肝障害患者の急性期と回復期における血漿脂質メタボロームのOPLS-DA解析による判別

(A)肝細胞障害型の薬物性肝障害9患者15サンプルによるスコアプロット



(B)肝細胞障害型の薬物性肝障害9患者15サンプルによるsプロット

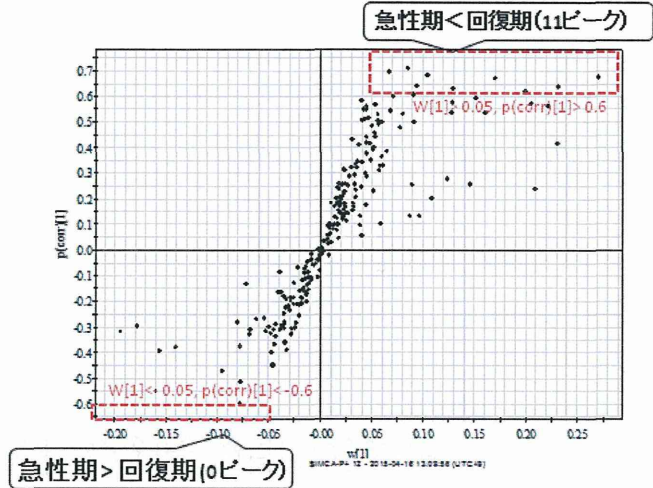


図4 OPLS-DAプロットより見出された肝細胞障害型の薬物性肝障害の急性期と回復期を判別するバイオマーカー候補(リン脂質、スフィンゴ脂質)

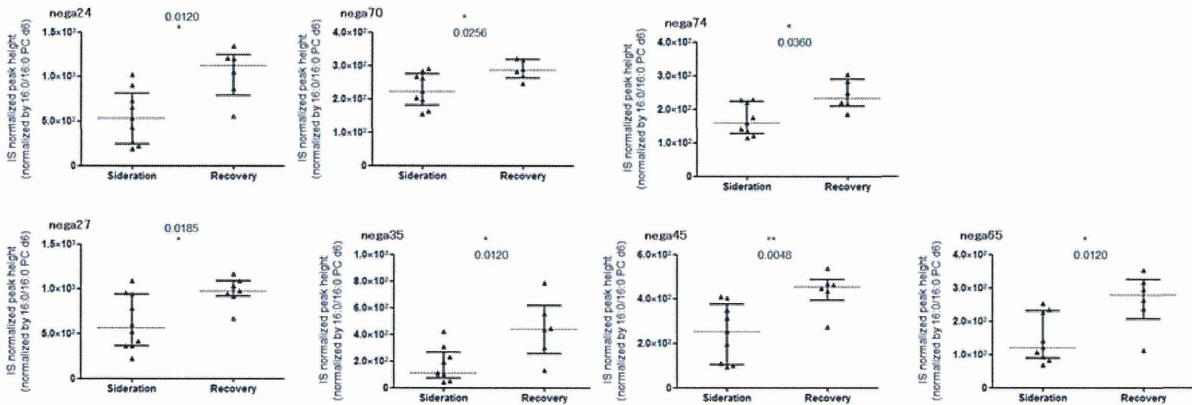
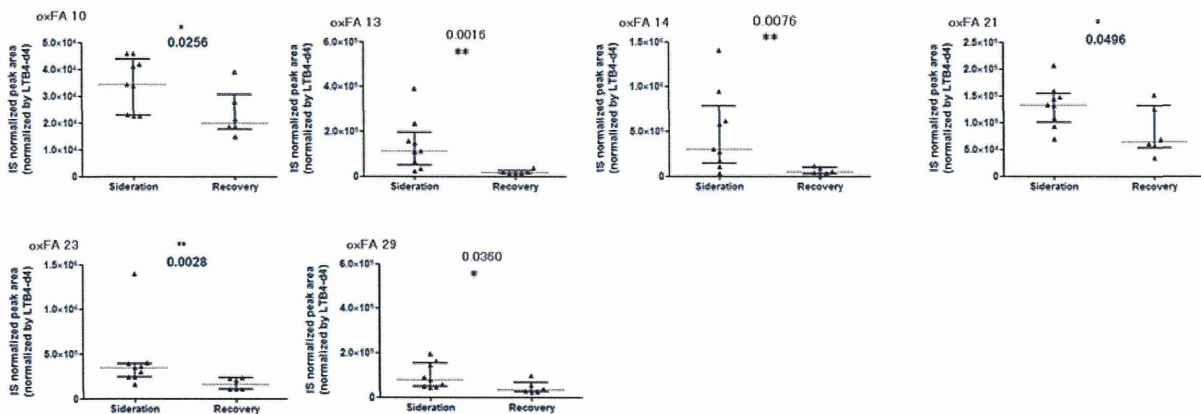


図5 肝細胞障害型の薬物性肝障害の急性期と回復期を判別するバイオマーカー候補(酸化脂肪酸)



III. 研究成果の刊行に関する一覧表と別刷

研究成果の刊行に関する一覧表

書籍

| 著者氏名 | 論文名 | 書籍全体の編集者名 | 書籍名 | 出版社名 | 出版地 | 出版年 | ページ |
|-----------------|------------------------------|-----------------|----------------------------------|-----------|-----|------|--------------|
| 熊谷雄治 | 国内臨床試験における心臓安全性評価の現状と将来 | 安全性評価研究会編集企画委員会 | 谷本学校毒性質問箱 | サイエンティスト社 | 東京都 | 2012 | 14巻 20-35 |
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| 鈴木孝昌 | 網羅的な発現をみるマイクロアレイ解析との比較を例に | 北條浩彦 | 実験医学別冊 原理からよくわかるリアルタイムPCR完全実験ガイド | 羊土社 | 東京 | 2013 | 111-121 |
| 鈴木孝昌 | コンパニオン診断薬の現状と課題 | | 最先端バイオマーカーを用いた診断薬/診断装置開発と薬事対応 | 技術情報協会 | 東京 | 2015 | 271-275 |

雑誌

| 著者氏名 | 論文名 | 雑誌名 | 巻 | ページ | 刊行年 |
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| Watanabe T, Suzuki T, Natsume M, Nakajima M, Narumi K, Hamada S, Sakuma T, Koeda A, Oshida K, Miyamoto Y, Maeda A, et al. | Discrimination of genotoxic and non-genotoxic hepatocarcinogens by statistical analysis based on gene expression profiling in the mouse liver as determined by quantitative real-time PCR | Mutat Res | 747 | 164-175 | 2012 |
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| 斎藤嘉朗、前川京子、田島陽子、児玉進、黒瀬光一 | 市販後安全性確保に係るバイオマーカーと診断 | レギュラトリーサイエンス学会誌 | 3 | 43-55 | 2013 |

| | | | | | |
|---|--|------------------------|-----|-----------|------|
| Suenaga K, Takasawa H, Watanabe T, Wako Y, Suzuki T, Hamada S, Furihata C | Differential gene expression profiling between genotoxic and non-genotoxic hepatocarcinogens in young rat liver determined by quantitative real-time PCR and principal component analysis | Mutat Res | 751 | 73-83 | 2013 |
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| 斎藤嘉朗, 前川京 子, 齊藤公亮, 佐藤 陽治, 鈴木孝昌 | タンパク質・内在性代謝物バイ オマーカーを利用した医薬品 開発の活性化にむけて | 国立医薬品食 品衛生研究所 報告 | 131 | 20-24 | 2013 |
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