| スコア順位 | | Description | GI | 分子量 | システイン残基数 | Ratio | | Score(H) | | Score(L) | | Protein Coverage(H) | | Protein Coverage(L) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| A47 | QSTAR | | | | | A47 | QSTAR | A47 | QSTAR | A47 | QSTAR | A47 | QSTAR | A47 | QSTAR |
| 276 | | myosin XV; unconventional myosin-15 | gi\|22547229 | 395219.5 | 45 | N/A | | | | 20.2 | | | | 0 | |
| 277 | | chemokine (C-C motif) receptor 8; chemokine (C-C) re | gi\|4885121 | 40844.4 | 14 | N/A | | | | 20.2 | | | | 2 | |
| 278 | | PERQ amino acid rich, with GYF domain 1; postmeiotic | gi\|12007656 | 89740.9 | 10 | N/A | | | | 20.2 | | | | 1 | |
| 279 | | vacuolar protein sorting 29 isoform 1; vacuolar sorting | gi\|7706441 | 20505.7 | 3 | 0.72 | | | | 20.2 | | | | 3 | |
| 280 | | hypothetical protein MGC48986 | gi\|28557703 | 31064.9 | 7 | N/A | | | | 20.1 | | | | 5 | |
| 281 | | D site of albumin promoter (albumin D-box) binding pro | gi\|31542493 | 34348.9 | 2 | 0.57 | | 20.1 | | | | 5 | | | |
| 282 | | transducin-like enhancer protein 2; transducin-like enh | gi\|21361151 | 79841.0 | 21 | 0.80 | | 16.1 | | 20.1 | | 2 | | 2 | |
| 283 | | hypothetical gene MGC16309 | gi\|15529980 | 35339.8 | 6 | 0.61 | | 20.0 | | | | 7 | | | |
| 284 | | splicing factor, arginine/serine-rich 1 (splicing factor 2, | gi\|5902076 | 27744.6 | 2 | 1.79 | | 20.0 | | | | 6 | | | |
| 285 | | super conserved receptor expressed in brain 3 | gi\|9507143 | 41481.4 | 15 | N/A | | | | 20.0 | | | | 5 | |
| 286 | | hypothetical protein XP_211108 | gi\|27479549 | 10737.5 | 5 | 1.41 | | | | 20.0 | | | | 17 | |

その結果、本画分(SCX50画分)をABI-4700で解析し、Rank 1でPeptideでのMascot scoreが30以上のものを選択すると、158種類のたんぱく質の同定と比較定量が可能であり、Peptide Score を 20 以上とすると、約 286 種類が同定・定量された。一方、同様に SCX50 画分を C18-nanoLC/Q-Star system で解析した場合は、Rank 1, Peptide Score が 20 以上のものを選択すると、119 種類のたんぱく質が同定および定量が可能であった。なお、ここでいう「同定」とは、Mascot によって基準以上のスコアでヒットしたことを意味しており、偽陽性の結果の排除等の精査を経た最終的な同定数については、別途検討する必要がある。
また、殆どのたんぱく質のH鎖標識/L鎖標識比（比較定量値）は約1であったので、cICAT 法による比較定量法は基本的には満足するものと考えられた（後述）。しかし、一部のものはScoreが低いときは、定量値が1より大きくずれるものがあった。このような場合は、データを詳細に再検討すると、他のペプチドがスペクトル上で重複している場合が多かった。

ABI-4700 でのトップ 119 種類と Q-Star でのトップ 119 種類を比較検討したところ、両者の共通なたんぱく質は 80 種類であり、Q-Star でのみ同定・定量されたのものが 39 種類、ABI-4700 でのみ同定・定量されたのものが 39 種類であり、どちらか一つでも同定・定量されたものは合計 158 種類であった（図 9 A)。　一方、ABI-4700 および Q-Star で Score が 20 以上のものを選択すると、両者で共通なものは 94 種類、Q-Star でのみ同定されたものが 25 種類、ABI-4700 でのみ同定されたものが 192 種類であり、どちらか一つでも同定されたものは合計 311 種類であった（図 9 B)。

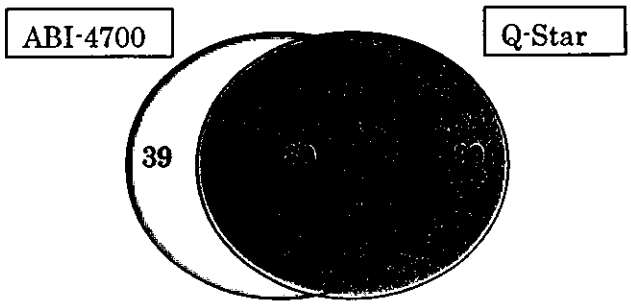


図９A.　Diagrammatic Representation of Top 1-119 Proteins Detected in Normal Human Serum by Q-Star XL and ABI-4700 System

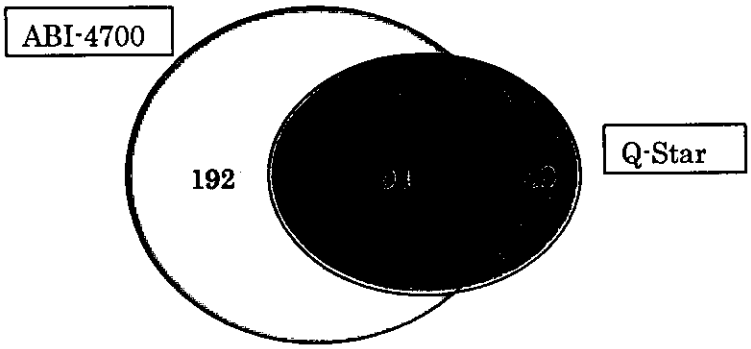


図９B.　Diagrammatic Representation of All proteins Detected in Normal Human Serum by Q-Star XL and ABI-4700 System

図１０，１１は、それぞれQ-StarおよびABI-4700のランク(#1-119) 種類までのたんぱく質種類のカテゴリー分類を示す。 いずれの場合も、上位は、すでに血清中に存在が報告されている、補体たんぱく質系、線溶・凝固たんぱく質系、血清糖たんぱく質系、結合たんぱく質系、リポたんぱく質系、接着たんぱく質系、プロテアーゼ系、プロテアーゼインヒビター系、キニン系等などであった。また、Q-StarとABI-4700ではカテゴリー分類（上位119種類に関して）に、

特に大きな差はなかった。

一方、ABI-4700 のランク(#1~119)と，ランク(#120 ~200)、ランク(#201~286)までのカテゴリー分類を比較すると(Data not shown)、ランクがさがるにつれて、補体、線溶・凝固系のたんぱく質は減っていき、その代わり、おそらくは細胞内からリークしたと思われるより微量な各種細胞質構造たんぱく質、プロテインカイネース系、プロテインホスファターゼ系、核内受容体関連たんぱく質系、機能不明たんぱく質等が増加する傾向が観察された。

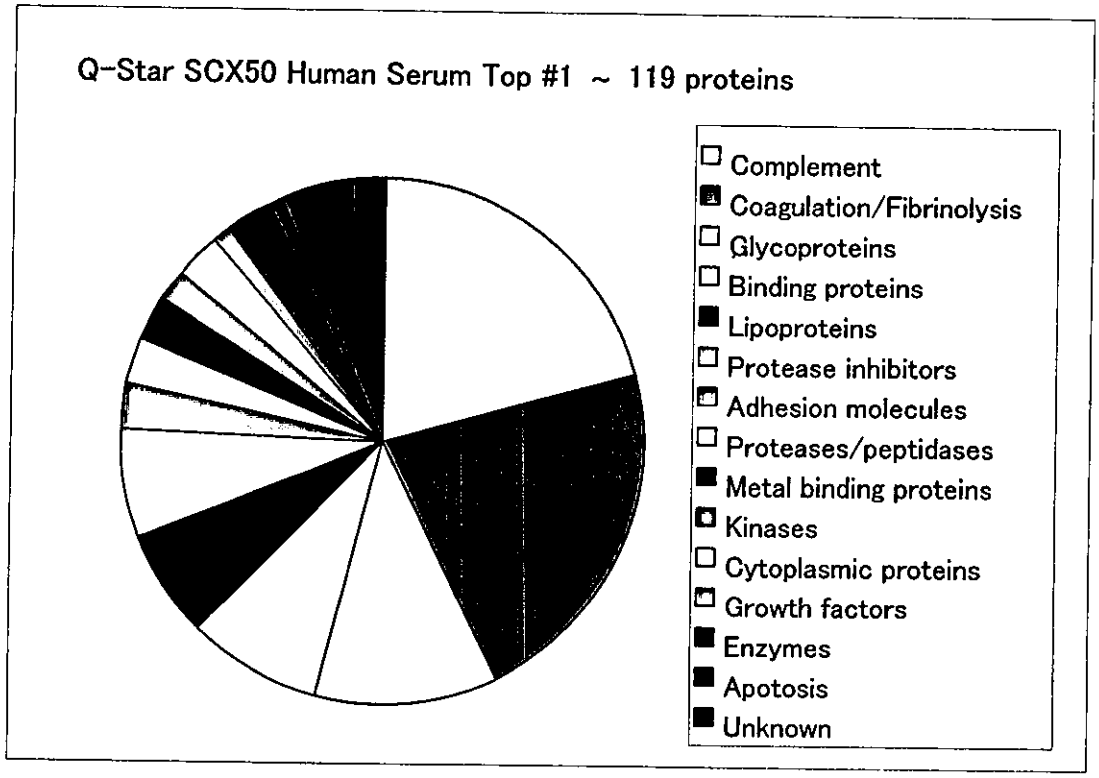


図10. Categories of Top # 1~119 Proteins Detected in Normal Human Serum by Q-Star XL System.

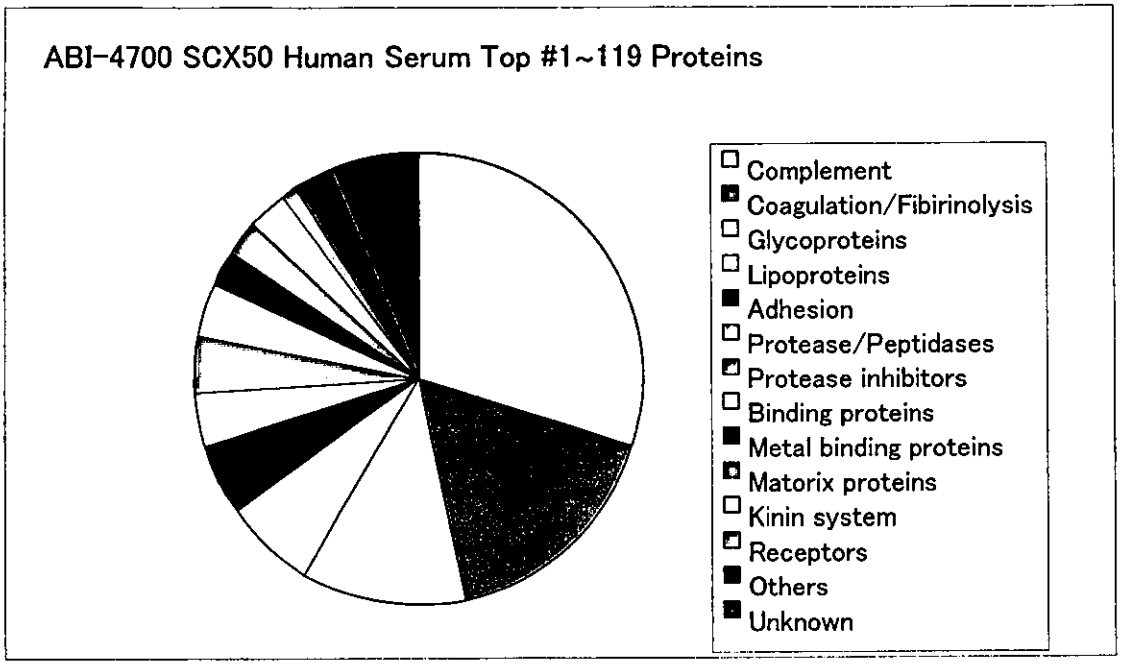


図１１. Categories of Top # 1~119 Proteins Detected in Normal Human Serum by ABI-4700 System.

さて、cICAT 試薬はたんぱく質中の Cys 残基に特異的に反応するとされる。従って、たんぱく質のモル濃度が高く、かつ Cys 含有ペプチドが多いほど良く反応し、同定の Score 値は高くなると考えられる。すなわち、濃度が高くても Cys 含有ペプチドが少なければ Score 値は低く、逆に濃度が低くても Cys 含有ペプチドが多ければ、Score 値は高くなる。　そこで、表２の中から、血中濃度がすでに測定されている補体系たんぱく質と線溶・凝固系たんぱく質を選択（表３）、各たんぱく質（H 鎖標識＋L 鎖標識）の同定 Score (S)と、その血清モル濃度(C (μM))およびその Cys 残基数(N)との関係を調べた（図１１，１２）。その結果、Score (S)を Y 軸に、モル濃度(C) × Cys 残基(N)(:Cys モル濃度)を X 軸のプロットしたところ、ABI-4700 でも Q-Star を用いた場合でも、Y と X 値は正の相関が見られた(ABI-4700: $Y = 11.6X + 263$, $R^2 = 0.74$, 図１１), Q-Star: $Y = 6.86X + 172$, $R^2 = 0.69$, 図１２)。このことは上述の推論を支持するものである。

## 表 3. 主要血清たんぱく質の濃度(C)・Cys 残基数(N)および Mascot スコア(S)

| たんぱく質名 | 血中濃度 (C) (μM) | システイン数(N) | C×N | スコア (ABI-4700) | スコア (Q-Star) |
|---|---|---|---|---|---|
| complement component 1, q subcomponent, alpha | 2.6 | 5 | 13.2 | 17.7 | 38.4 |
| complement component 1, q subcomponent, beta | 2.6 | 4 | 10.5 | 11.9 | 48.4 |
| complement component 1, q subcomponent, gamma | 2.6 | 4 | 10.5 | 114.0 | 15.3 |
| complement component 1, r subcomponent | 1.3 | 27 | 35.8 | 892.6 | 565.5 |
| complement component 1, s subcomponent | 1.3 | 27 | 35.8 | 484.8 | 251.3 |
| complement component 2 | 0.23 | 24 | 5.46 | 64.0 | 126.5 |
| complement component 3 | 6.7 | 27 | 180.0 | 2039.2 | 1225.3 |
| complement component 4 | 1.9 | 27 | 51.4 | 1021.8 | 354.2 |
| complement component 5 | 0.44 | 30 | 13.3 | 443.4 | 151.5 |
| Complement component 6 | 0.47 | 64 | 30.0 | 598.5 | 392.1 |
| complement component 7 | 0.41 | 56 | 23.1 | 1274.2 | 583.7 |
| complement component 8, alpha | 0.33 | 30 | 9.80 | 705.3 | 340.2 |
| complement component 8, beta | 0.33 | 30 | 9.80 | 193.4 | 189.6 |
| complement component 8, gamma | 0.33 | 3 | 0.980 | 55.2 | 122.0 |
| complement component 9 | 0.76 | 26 | 19.7 | 321.0 | 150.8 |
| complement factor B | 3.2 | 24 | 77.4 | 682.0 | 560.4 |
| complement factor D | 0.065 | 9 | 0.587 | 57.8 | |
| complement factor H | 3.2 | 82 | 264.5 | 3164.8 | 1774.8 |
| I factor (complement) | 0.56 | 42 | 23.3 | 1052.7 | 610.0 |
| plasminogen | 2.5 | 48 | 118.5 | 2260.1 | 1614.1 |
| coagulation factor II precursor; prothrombin | 1.4 | 26 | 36.1 | 2056.8 | 1383.4 |
| coagulation factor V precursor; labile factor; factor V Leiden | 0.20 | 20 | 4.00 | 143.8 | 105.9 |
| coagulation factor X precursor; prothrombinase; factor Xa | 0.20 | 24 | 4.80 | 180.5 | 44.4 |
| coagulation factor IX; Coagulation factor IX (plasma thromboplastic component) | 0.091 | 24 | 2.18 | 77.0 | 30.2 |
| Coagulation factor VIII VWF (von Willebrand factor) | 0.037 | 234 | 8.67 | 173.8 | |

文献（稲井眞彌・井上公蔵・田村昇共著医歯薬出版株式会社・補体学など）より得た各たんぱく質の分子量および血中濃度（μg/ml）より算出した血中のモル濃度 C(μM)およびアミノ酸配列情報から算出した Cys 残基数(N)および両者の積(C×N)と ABI4700 と Q-Star の測定結果に対する Mascot 検索を実施して得たスコア(S)を示した。Mascot 検索は HiSpec 上で実施しているため実際は ICAT-light と ICAT-heavy の標識ペプチドのスコア値が別々に算出されている。表中のスコアは両スコアを合算している。

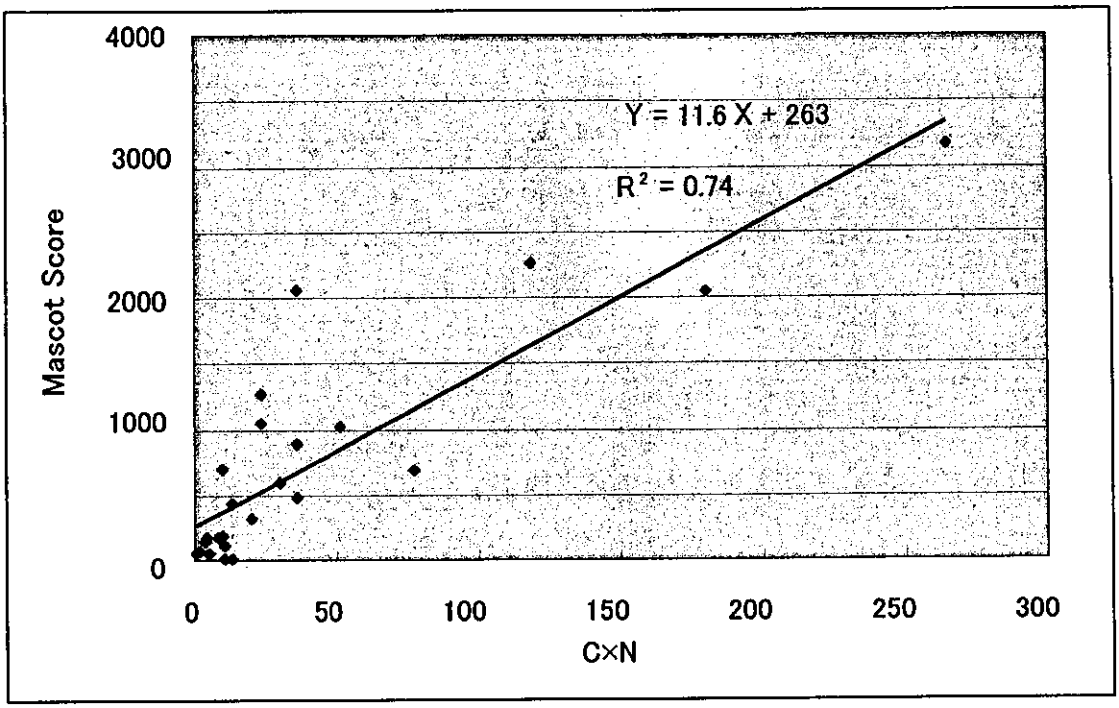


図11. Correlation between Mascot Score and Cys Concentration (C x N) of Proteins in Serum Detected by ABI-4700 System.

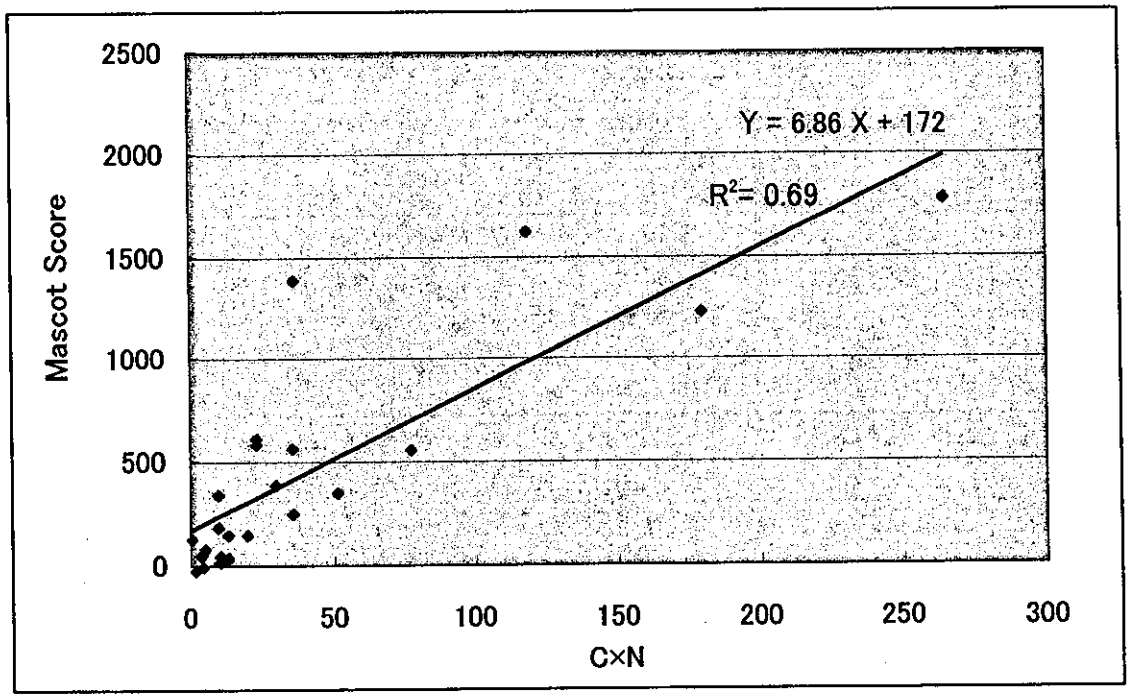


図12. Correlation between Mascot Score and Cys Concentration (C x N) of Proteins in Serum Detected by Q-Star XL System.

4）Spike sample(Lactoglobulin)を用いたICAT比較定量解析

前述のように、殆どの血清中のたんぱく質のH鎖/L鎖比（比較定量値）は約１であったので、cICAT法による比較定量法は基本的には満足するものと考えられる。このことをさらに確実にするために、血清中に既知量のSpike sample（Lactoglobulin)の量比を2～40倍に変えて添加したサンプルを、それぞれH鎖試薬、L鎖試薬で標識し、比較定量解析を行った（HiSpec ICAT比較定量ソフトを使用)。その結果、血清たんぱく質は前述と同様に殆どH鎖とL鎖の量比（H/L鎖比）は約１であったが、SpikeしたLactoglobulinの同定ICATペプチド（WENDECAQK）の量比は、2～20倍までのスパイク比と直線関係であり、ほぼ正確なICAT比較定量結果を示した（表４、図１３)。このことは、cICAT法はスペクトルの重なりやIntensityの弱いものを除けば、2～20倍の発現差であれば正確に比較定量が可能であることを示すと考える。

表４．Spike sample(Lactoglobulin)を用いたHiSpec(ICAT比較定量ソフト)によるICAT比較定量解析

*ABI-4700のcICAT比較定量結果*

| Description | Peptide Sequence | 測定値1 (H//L) | 測定値2 (H/L) | 平均値(H/L) | Spike比 (H/L) |
|---|---|---|---|---|---|
| lactoglobulin, beta | WENDECAQK | 1.39 | 1.18 | 1.29 | 1.5 |
| lactoglobulin, beta | WENDECAQK | 2.14 | 2.33 | 2.23 | 2 |
| lactoglobulin, beta | WENDECAQK | 3.89 | 4.09 | 3.99 | 5 |
| lactoglobulin, beta | WENDECAQK | 8.34 | 9.60 | 8.97 | 10 |
| lactoglobulin, beta | WENDECAQK | 20.13 | 17.34 | 18.74 | 20 |
| lactoglobulin, beta | WENDECAQK | 28.99 | 35.27 | 32.13 | 40 |

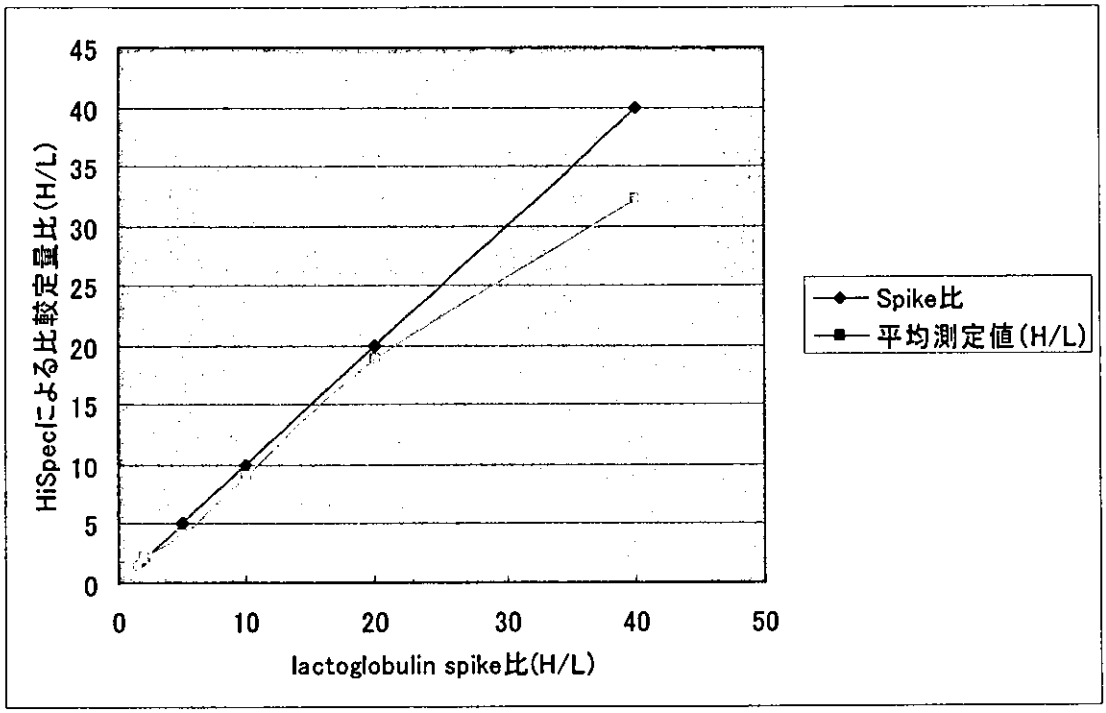


図１３．ICAT 比較定量ソフト（HiSpec）による ICAT 比較定量比と Spike 比との関係

**E．考察：**

本年度は、施設内の倫理審査委員会、個人情報保護のための匿名化システム、試料機器管理システム（LIMS）、情報セキュリティシステムを構築することで、研究協力機関からの臨床試料の受け入れ体制を整えたと考える。また、ヒト標準血清を用いて、同位体標識法（cICAT 法）、前処理法、質量分析法、大量たんぱく質同定法を含む一連の解析システムを検討した結果、本システムが血清疾患関連たんぱく質（トップ#1～100 種類）解析に有効な方法であると考えた。今後はさらに、ハイスループット性の高く、感度が高い解析システムを完成させ、研究協力機関より提供される患者臨床試料（血清）の解析に望みたい。なお、cICAT 試薬は、血清中のたんぱく質中の Cys 残基数（モル濃度）に比例して反応することが確認された。従って、微量成分であり Cys 残基数が少ないたんぱく質は、そのままでは同定・定量が困難であると予想されるので、限外ろ過法などの手段で微量成分を濃縮した上で、cICAT 法を用いた微量成分の解析研究を行いたい。また、今後、他の同位体標識試薬や iTRAQ 試薬等の新しい解析技術も必要であれば検討する。

F．結論：

研究協力機関からの臨床試料の受け入れために必要な施設内の倫理審査委員会、個人情報保護のための匿名化システム、試料機器管理システム（LIMS）を確立した。　ヒト標準血清を用いる同位体標識法（cICAT 法）を検討し、血清前処理法(主要たんぱく質の除去)、cICAT peptide の分離法、nano-LC system/高性能質量分析(Q-Star XL, ABI-4700 等）解析法、および大量たんぱく質同定・定量解析法(HiSpec System)までの一連の血清疾患関連たんぱく質解析フローをほぼ完成させた。　本システムは、血清疾患関連たんぱく質（トップ#1～100 種類）の同定と比較定量（発現差解析）に有効な方法であると考える。

G. 健康危険情報：

特になし。PF では万全なバイオハザード対策設備を施工している。

H. 研究発表：

なし。

I. 知的財産権の出願・登録状況：

1．特許取得：

なし。

2．実用新案登録：

なし。

3．その他

K. 参考文献：

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