**Supplementary Content**

1. **Association of Patient Characteristics with Test Classification**

Supplementary Table 1: Patient characteristics by test classification within the development set

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  | Resistant (N=85)  n (%) | Sensitive (N=34)  n (%) | P value |
| Gender | Male | 52 (61) | 20 (59) | 0.835 |
|  | Female | 31 (36) | 14 (41) |  |
| Dose, peptide | 1 mg/kg, yes | 4 (5) | 5 (15) | 0.245 |
| vaccine | 3 mg/kg, yes | 29 (34) | 13 (38) |  |
|  | 10 mg/kg, yes | 9 (11) | 2 (6) |  |
|  | 3 mg/kg, no | 43 (51) | 14 (41) |  |
| Prior Ipilimumab | No | 21 (25) | 10 (29) | 0.647 |
|  | Yes | 64 (75) | 24 (71) |  |
| PD-L1 expression  (5% tumor) | Positive | 5 (6) | 3 (9) | 0.704 |
| Negative | 22 (26) | 7 (21) |  |
| NA | 58 (68) | 24 (71) |  |
| Serum LDH levels | > 2ULN | 28 (34) | 3 (9) | 0.006 |
|  | < 2ULN | 56 (66) | 31 (91) |  |
|  | median  range | 499  180-4914 | 469  149-3043 | 0.034\* |
| Age | ≥ 65 | 39 (46) | 10 (29) | 0.148 |
|  | < 65 | 46 (54) | 24 (71) |  |
|  | median  range | 64  23-87 | 60  16-74 | 0.039\* |
| Baseline tumor size | < median | 33 | 27 | < 0.001 |
|  | ≥ median | 52 | 7 |  |
| Baseline tumor size | median | 31.82 | 9.97 | < 0.001\* |
|  | range | 1.92-259.03 | 0.88-88.24 |  |

P values are for Fisher’s exact test, except for \* which are Mann-Whitney p values

1. **Association of Test Classification with Immune Adverse Events**

Supplementary Table 2: Patient characteristics by test classification within the development set

|  |  |  |  |
| --- | --- | --- | --- |
|  | Sensitive (N=34) | Resistant (N=85) | P value |
| No or only grade 1-2 Immune Adverse Event | 33 | 77 | 0.443 |
| Grade 3-4 Immune Adverse Event | 1 | 8 |  |

1. **Method of Assessment of PD-L1 expression**

PD-L1 staining was done using the DAKO antibody as discussed in Weber J et al, J Clin Oncol 2013 31:34, 4311-4318, reference in the manuscript. The immunohistochemistry assay for programmed death-ligand 1 (PD-L1) incorporated an anti–PD-L1 rabbit monoclonal antibody (clone 28-8), which was developed on an automated platform by Dako North America (Carpinteria, CA). Consecutive sections were stained for PD-L1 and a negative control reagent to control for nonspecific staining. All sections were independently read by two pathologists, with final scores confirmed through an adjudication process. A sample was deemed PD-L1 positive for membranous staining by two alternative definitions: if ≥ 5% or 1% of tumor cells, in a minimum of 100 evaluable tumor cells, had observable PD-L1–positive staining at any intensity*.*

1. **Sample Preparation and Acquisition of Mass Spectra**

**Sample Preparation**

Samples were thawed and 3 μl aliquots of each test sample and quality control/reference serum (a pooled sample obtained from serum of five healthy patients, “SerumP3”) spotted onto serum cards (Therapak). The cards were allowed to dry for 1 hour at ambient temperature after which the whole serum spot was punched out with a 6mm skin biopsy punch (Acuderm). Each punch was placed in a centrifugal filter with 0.45 µm nylon membrane (VWR).  One hundred μl of HPLC grade water (JT Baker) was added to the centrifugal filter containing the punch. The punches were vortexed gently for 10 minutes then spun down at 14,000 rcf for two minutes. The flow-through was removed and transferred back on to the punch for a second round of extraction. For the second round of extraction, the punches were vortexed gently for three minutes then spun down at 14,000 rcf for two minutes. Twenty microliters of the filtrate from each sample was then transferred to a 0.5 ml eppendorf tube for mass spectral analysis.

All subsequent sample preparation steps were carried out in a custom designed humidity and temperature control chamber (Coy Laboratory). The temperature was set to 30 °C and the relative humidity at 10%.

An equal volume of freshly prepared matrix (25 mg of sinapinic acid per 1 ml of 50% acetonitrile:50% water plus 0.1% TFA) was added to each 20µl serum extract and the mix vortexed for 30 sec. The first three aliquots (3 x 2µl) of sample:matrix mix were discarded into the tube cap. Eight aliquots of 2µl sample:matrix mix were then spotted onto a stainless steel MALDI target plate (SimulTOF).  The MALDI target was allowed to dry in the chamber before placement in the MALDI mass spectrometer.

**Spectral Acquisition**

Spectra were obtained using a MALDI-TOF mass spectrometer (SimulTOF 100 s/n: LinearBipolar 11.1024.01 from Virgin Instruments, Sudbury, MA, USA). The instrument was set to operate in positive ion mode, with ions generated using a 349 nm, diode-pumped, frequency-tripled Nd:YLF laser operated at a laser repetition rate of 0.5 kHz. External calibration was performed using a mixture of standard proteins (Bruker Daltonics, Germany) consisting of insulin (*m/z* 5734.51 Da), ubiquitin (*m/z*, 8565.76 Da), cytochrome C (*m/z* 12360.97 Da), and myoglobin (*m/z* 16952.30 Da).

Spectra from each MALDI spot were collected as 800-shot spectra that were 'hardware averaged' as the laser fires continuously across the spot while the stage is moving at a speed of 0.25 mm/sec. A minimum intensity threshold of 0.01 V was used to discard any 'flat line' spectra. All 800-shot spectra with intensity above this threshold were acquired without any further processing.

1. **Spectral Processing**

Spectral processing is necessary for two main reasons. First, it is used to average together many of the 800-shot ‘raster’ spectra that were collected on the mass spectrometer to create the Deep MALDI1 averages. This allows a deeper and less noisy probing of the serum proteome. Second, spectral processing was essential to render the deep MALDI average spectra reproducible and comparable across samples.

**Processing of Raster Spectra to Deep MALDI averages**

Raster spectra wewre rescaled in the mass/charge (m/Z) axis relative to a standard reference spectrum to correct for any overall alignment issues in m/Z. To improve the signal to noise ratio of the spectra, a ripple filter was then applied. For a finer adjustment of alignment in the m/Z axis, background was subtracted from the raster spectra and peaks are located. This peak list was then used to align raster spectra prior to background subtraction, using a set of 43 fixed alignment points, Supplementary Table 2.

Supplementary Table 3: Points in m/Z used to align the raster spectra

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| 3168 | 7202 | 8919 | 12173 | 15127 | 28298 |
| 4153 | 7563 | 8994 | 12572 | 15263 | 33500 |
| 4183 | 7614 | 9133 | 12864 | 15869 | 67150 |
| 4792 | 7934 | 9310 | 13555 | 17253 |  |
| 5773 | 8034 | 9427 | 13763 | 18630 |  |
| 5802 | 8206 | 10739 | 13882 | 21066 |  |
| 6433 | 8684 | 10938 | 14040 | 23024 |  |
| 6631 | 8812 | 11527 | 14405 | 28090 |  |

The raster spectra were then filtered to keep only spectra where at least 20 peaks were found and at least 5 of the alignment points in Supplementary Table 1 were used in their alignment. Deep MALDI, 400,000 laser-shot averages were then created by averaging together 500 randomly selected from the pool of filtered raster spectra.

**Processing of Deep MALDI Average Spectra**

“Spectrum” refers to a Deep MALDI average spectrum. The background in each spectrum was estimated and subtracted. Spectra were then normalized in several stages. First, a coarse normalization was performed using a partial ion current (PIC) approach using regions of the spectra that showed low variability across the population of interest and that showed no sign of association with outcomes. Spectral regions known to be intrinsically unstable were excluded from the regions used for normalization. The regions used in this normalization step were defined using the development set of spectra and then held fixed as fully specified parameters of the test. For each spectrum the area under the spectra within each m/Z region used for normalization was calculated and summed to produce a normalization coefficient. Each spectrum was then divided by its own normalization coefficient to yield the normalized spectrum. Supplementary Table 3 gives the upper and lower limits in m/Z of the regions used in normalization.

Supplementary Table 4: m/Z regions used for coarse normalization

|  |  |
| --- | --- |
| **Lower limit m/Z** | **Upper limit m/Z** |
| 3530.679 | 3784.658 |
| 3785.029 | 4078.739 |
| 4220.21 | 4323.065 |
| 4875.581 | 4943.903 |
| 5260.635 | 5435.524 |
| 5436.47 | 5682.433 |
| 6050.421 | 6376.807 |
| 6510.852 | 6601.081 |
| 7751.414 | 7898.826 |
| 10606.12 | 10897.2 |
| 10908.61 | 11356.51 |
| 12425.27 | 12527.26 |
| 17710.35 | 18504.69 |
| 19212.92 | 20743.82 |
| 22108.95 | 22959.15 |
| 23738.5 | 24739.04 |

Using the normalized spectra, a second finer PIC normalization was carried out after a check on the variability of the normalized spectra and any dependence on outcome. The m/Z regions used in the second normalization step are given in Supplementary Table 4.

Supplementary Table 5: m/Z regions used for finer normalization

|  |  |
| --- | --- |
| **Lower limit m/Z** | **Upper limit m/Z** |
| 4168.226 | 4219.839 |
| 4875.581 | 4943.903 |
| 4946.131 | 5077.576 |
| 5080.918 | 5259.892 |
| 5260.635 | 5435.524 |
| 6510.852 | 6601.081 |
| 7751.414 | 7898.826 |
| 10606.12 | 10897.2 |
| 10908.61 | 11356.51 |

Although the spectral alignment is typically very good, due to the alignment carried out in the raster processing, the spectra were aligned to address minor differences in peak positions that might still be present. This was carried out using a fixed set of alignment points, which are listed in Supplementary Table 5.

Supplementary Table 6: Points in m/Z used to align the spectra

|  |  |  |  |
| --- | --- | --- | --- |
| 3315 | 8916 | 15872 | 28293 |
| 4153 | 9423 | 16078 | 67150 |
| 4457 | 9714 | 17256 |  |
| 4710 | 12868 | 17383 |  |
| 5066 | 13766 | 18631 |  |
| 6433 | 14045 | 21069 |  |
| 6631 | 14093 | 21168 |  |
| 7934 | 15131 | 28084 |  |

Features were defined in the mass spectra. These were defined by visual inspection of an indication representative set of spectra. A feature is an m/Z region in the mass spectrum, specified by its lower m/Z limit and its upper m/Z limit. While features were defined based on the location of mass spectral peaks in typical spectra, for any individual spectrum the feature may or may not contain a well-defined mass spectral peak. Once the features were defined, they became parameters in the fully-specified test. For each feature and spectrum a feature value was defined as the integrated area under the spectrum within the feature. For this test 351 features were defined, although not all were used by the classification algorithm.

To ensure that spectral data can be reproducibly generated, the QC/reference samples that were included at the beginning and end of each batch of samples run were used to batch correct the feature values of each batch of samples. Batch correction parameters were determined by comparing the feature values of the QC/reference samples within the batch to gold standard values for the QC/reference sample defined from those contained within the first batch of the development set samples that were run. Note that development set samples and test samples were not used in determining batch correction parameters. Once the batch correction parameters awere obtained for a particular batch, all feature values for each spectrum in the batch were corrected. This process adjusted for small m/Z dependent changes in mass spectral performance of the mass spectrometer or between mass spectrometers.

The final step in processing of the spectra was another PIC normalization step. Using the development set of spectra a subset of the 351 defined features was defined for final spectral normalization that had low coefficients of variation and were not associated with any of the clinical outcome variables in the development set. The m/Z regions (also features) used and fixed as parameters in the fully-specified test are listed in Supplementary Table 6.

Supplementary Table 7: m/Z regions used for final normalization

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Lower limit m/Z** | **Upper limit m/Z** |  | **Lower limit m/Z** | **Upper limit m/Z** |
| 3230.73 | 3254.516 |  | 6603.961 | 6619.26 |
| 3255.103 | 3274.191 |  | 6648.512 | 6665.64 |
| 3405.16 | 3435.407 |  | 6668.623 | 6692.68 |
| 3531.431 | 3576.36 |  | 6719.237 | 6744.063 |
| 3665.631 | 3692.941 |  | 7067.293 | 7080.287 |
| 3942.253 | 3964.571 |  | 8897.436 | 8905.873 |
| 3994.23 | 4023.008 |  | 9010.011 | 9030.58 |
| 4393.817 | 4423.436 |  | 9030.764 | 9045.668 |
| 4880.953 | 4901.401 |  | 10615.84 | 10657.79 |
| 5053.556 | 5082.123 |  | 12716.47 | 12759.57 |
| 5087.535 | 5120.613 |  | 12761.24 | 12810.35 |
| 5395.905 | 5410.94 |  | 13929.87 | 13956.27 |
| 6184.807 | 6201.069 |  | 14076.2 | 14118.97 |
| 6408.625 | 6467.033 |  | 14178.77 | 14219.19 |
| 6577.691 | 6601.17 |  | 14231.55 | 14277.66 |

The final normalization coefficient was calculated for each spectrum and all feature values were divided by the normalization coefficient for the spectrum/sample to produce the final processed feature values. These were the feature values that were used for the development set samples for the creation of the test and these would be the feature values that would be input into the test classification algorithm when performing the fully specified test on a new sample.

1. **Development of the Classification Algorithm**

**General Approach to Identifying a Patient Subgroup with Particularly Good Outcome**

As the goal of this study was to develop a test able to identify patients likely to have durable benefit from therapy, i.e. patients with particularly good outcomes, a strategy of creating multiple classifiers and demanding that all of them return a good prognosisc classification for a sample to be classified into this group was adopted. Each of the multiple classifiers was developed using a clinically different subset of the development set of samples and the requirement that they all have to identify a test sample as being associated with good prognosis for the sample to be classified as ‘sensitive’ means that the sample hasd to display a good prognosis molecular profile across all of the subset of samples with which we compared it.

We chose to select the clinically different subsets based on their tumor size using uni-dimentional linear measures of the five largest lesions determined by RECIST. At the time of test developement we had baseline tumor linear dimension for 104 of the 119 patients. Only the spectral data from the samples from these 104 patients were used in classifier development. The samples were ranked by tumor size from smallest to largest. The 50 samples with smallest tumors were defined as the development subset for subclassifier 1, and the remaining 54 samples with the largest tumors were defined as the development subset for subclassifier 7. To create 5 other subclassifiers, 50-10*i* samples (1 ≤ *i* ≤ 5) were selected from the 50 with the smallest tumors and combined with 10*i* samples from the 54 with the largest tumors. For each of these subsets of the development set, a subclassifier was created as explained in the following sections.

**A hierarchical classifier development platform designed for problems where the number of available instances is smaller than the number of measured attributes**

Each subclassifier was created using a hierarchical classifier development platform designed specifically to work well in settings where the number of attributes (features) measured for each instance (sample) exceeds the number of instances available for classifier training. This platform has been used in several other personalized medicine projects (e.g.,27, D. Mahalingam, W. Washburn, G. Halff, L. Chelis, S. Kakolyris, S. Vradelis, J. Grigorieva, C. Oliveira, H. Roder, and J. Roder, “A mass spectrometry based serum test for the detection of hepatocellular carcinoma (HCC) in high risk patients,” Cancer Res., vol. 75(15 suppl), Abstract 1567, Aug. 2015, J. Roder, J. Löffler-Ragg, R. Stauder, U. Germing, W. Sperr, P. Valent, H. Roder, A. Steingrimsson, and H. Zwierzina, “A mass spectrometry-based serum protein test for prognosis of patients with MDS.,” Cancer Res., vol. 75, no. 15 supplement, Abstract 5304, Aug. 2015) and a detailed description can be found in21. It incorporates aspects of traditional and modern machine learning, including bagging, boosting, and regularization using dropout, with the aim of producing classifiers with reliable performance estimates from relatively small sample sets while minimizing chances of overfitting to peculiarities in the development set data.

The platform structure is illustrated schematically in Supplementary Figure 1. The set of samples available for development was randomly split into training and test sets many times. This prevented the use of one training/test split that may be particularly easy or hard to classify in testing or particularly poor for training. An eventual ensemble average (“bagging”26) over these training/test split realizations allowed every sample in the development set to contribute to the performance estimate of the final classifier via an “out-of-bag” estimate (L. Breiman, “Out-of-bag estimation,”Technical Report, Department of Statistics, University of California, 1996. https://www.stat.berkeley.edu/~breiman/OOBestimation.pdf)

i.e. the classification for a given sample in the development set was evaluated only over the subset of realizations where the sample is in the test set and not in the training set. This allowed for more reliable and generalizable classifier performance estimates to be generated from the development set alone.

Supplementary Figure 1: Schema of the hierarchical classifier development platform



For each training/test split realization, many classifiers (“atomic classifiers”) were built using subsets of the mass spectral features. Here we used k-nearest neighbor classifiers with fixed k=9 for atomic classifiers and used all single features and all possible combinations of pairs of features chosen from a reduced feature subset determined via a bagged feature deselection process (described separately below). Each atomic classifier was applied to its training set and the accuracy of the resulting classification groups assessed. The atomic classifiers were filtered so that only classifiers demonstrating acceptable classification accuracy were used further in the platform. The performance of the individual atomic classifiers did not need to be excellent, as they were later combined. This approach uses the idea of boosting (R.E. Schapire, “The Strength of Weak Learnability,” Machine Learning, vol. 5, pp. 197-227, 1990) – that many classifiers of decent performance can be combined into an overall classifier with at least as good, or better, performance. The use of many atomic classifiers increases test robustness, again adding more protection against overfitting, as we were not selecting the few top performing classifiers or features based on their apparently superior performance on the training set.

Once the atomic classifiers were filtered and poorly performing classifiers eliminated, the remaining atomic classifiers were combined to create one base classifier per training/test split realization. This was done using logistic regression over the training set samples. As there were very many atomic classifiers that pass filtering, it is essential to employ a strong regularizer to avoid overfitting during the regression. We used the concept of dropout, a technique commonly used as the regularizer during the training of deep learning nets [20]. Our regularization method was implemented as follows. From the pool of atomic classifiers passing filtering, we randomly selected 10 atomic classifiers. We performed the logistic regression to calculate weights for combining this subset of atomic classifiers. We repeated this many times, enough that each atomic classifier was drawn many times, each dropout iteration drawing a random set of 10 atomic classifiers. The weight for each atomic classifier was averaged over many dropout iterations to give the weights for the final logistic combination. The continuous variable output of the logistic combination was converted to a single binary output by applying a threshold of 0.5.

The final level of the platform hierarchy was an ensemble average of the base classifiers (bagging over the training/test split realizations). This was carried out as a majority vote of binary outputs. In order to obtain meaningful performance estimates from the development set of samples, it was necessary to adapt the majority vote to an out-of-bag estimate, in which the majority vote for a particular sample was carried out only over the subset of base classifiers for which the sample was not included in the training set.

1. **Training Class Definition and a Semi-Supervised Approach to Simultaneous Refinement of Training Class Labels and Classifier**

This approach used supervised learning, i.e., it was necessary to know the training class labels for the classification problem, in this instance, which samples were from patients in the group likely to have durable benefit from immune therapy and which were not. It was not a priori clear how to unambiguously define durable benefit from time-to-event data in a way that revealed underlying information in the molecular data. We employed an approach that simultaneously refined training class labels for classifier development at the same time as the classifier itself. This is shown schematically in Supplementary Figure 2.

Supplementary Figure 2: Process for the simultaneous refinement of training class labels and classifier



First an educated guess was made for training class labels. The samples were sorted according to patient survival and the patients with the longest survival were assigned to the good prognosis group and the others to the poor prognosis group. Using these class labels, a classifier was constructed using the hierarchical approach explained above. Once the classifier was created, it was used to classify the samples in the development set or subset, with reliable and unbiased classifications obtained using its ‘out-of-bag’ approach. These classifications were used as the training class labels to create a second classifier, which reclassified the development subset samples, producing an iterative process. This typically converged either exactly or apart from very few samples after 10 or fewer iterations. The result was a classifier together with a consistent set of training labels for the development set.

1. **Bagged Feature Deselection**

The classifier development approach outlined here was constructed to minimize the chances of overfitting and to allow reliable assessments of classifier performance to be drawn from relatively small development sample sets. For this reason, feature selection was generally avoided. However, in problems where there were many features useful for the classification task it was often possible to prune the features used for classifier development to a reduced set by deselecting features that show little utility. This approach was used in the development of this test.

Prior to developing each classifier using the hierarchical platform method, the set of 351 available mass spectral features was pruned down to a smaller set by deselecting features with little apparent utility. The classifier development set or subset was randomly split many times into a training set and a holdout set as for hierarchical classifier development. For each of the 351 features a k-nearest neighbor (kNN) classifier (k=9) was created using the training set and this was applied to the training set samples. The classification accuracy of the kNN classifier on the training set was assessed and if it exceeded a certain threshold, the feature used was added to a list. This was repeated for all features within each training set realization and across many training set realizations. The cumulative list of features thus assembled was then analyzed. Features occurring very few times or not at all in the list were considered not likely to be useful for classification and were discarded to leave a pruned list of features that was then used within the hierarchical classification development platform. This process was repeated as the training class labels were updated in each iteration of the simultaneous training class label and classifier refinement process and the reduced feature sets defined in the final iteration were those used within the final test (56 features for subclassifier 1, 69 for subclassifier 2, 75 for subclassifier 3, 82 for subclassifier 4, 84 for subclassifier 5, 85 for subclassifier 6 and 85 for subclassifier 7). It was important to note that this process focused on deselecting features with little potential utility in classification and not on selecting the “best” features for their classification power. Hence, it was less prone, but still not immune, to lead to overfitting and given how the features were subsequently used within the hierarchical classifier development platform, the precise choice of cutoff to determine features of little utility had little or no impact on final classifier performance as long as it was selected conservatively in the spirit of a deselection.

1. **Protein Set Enrichment Analysis Proteins Sets for Associated Biological Functions**

Supplementary Table 8: Lists of proteins/peptides included in each of the significantly associated biological function protein sets

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Complement** | | **Acute Phase** | | **Wound Healing** | |
| **UNIPROT ID** | **Full Name of Protein/Peptide** | **UNIPROT ID** | **Full Name of Protein/Peptide** | **UNIPROT ID** | **Full Name of Protein/Peptide** |
| P02741 | C-reactive protein | P01308 | Insulin | Q6YHK3 | CD109 |
| P61812 | Transforming growth factor beta-2 | P02671 | D-dimer | P09038 | Basic fibroblast growth factor |
| P01023 | alpha2-Macroglobulin | P08697 | alpha2-Antiplasmin | P05121 | Plasminogen activator inhibitor 1 |
| P05155 | C1-Esterase Inhibitor | P00734 | Prothrombin | P04626 | erbB2 /HER2 |
| P02745 | Complement C1q | P00734 | Thrombin | P04275 | von Willebrand factor |
| P00736 | Complement C1r | P02741 | C-reactive protein | P01308 | Insulin |
| P09871 | Complement C1s | P01023 | alpha2-Macroglobulin | P02671 | D-dimer |
| P01024 | Complement C3 | P02743 | Serum amyloid P | P05019 | Insulin-like growth factor I |
| P01024 | Complement C3a anaphylatoxin | P11226 | Mannose-binding protein C | Q99075 | Heparin-binding EGF-like growth factor |
| P01024 | Complement C3b | P05231 | Interleukin-6 | P08697 | alpha2-Antiplasmin |
| P0C0L4 | Complement C4 | P01011 | alpha1-Antichymotrypsin | P00747 | Angiostatin |
| P0C0L5 | Complement C4b | P01009 | alpha1-Antitrypsin | P02649 | Apolipoprotein E |
| P01031 | Complement C5 | P02765 | alpha2-HS-Glycoprotein | P02649 | Apolipoprotein E (isoform E2) |
| P01031 | Complement C5a | P02751 | Fibronectin | P00740 | Coagulation factor IX |
| P01031 | Complement C5b,6 Complex | P00738 | Haptoglobin | P02675 | Fibrinogen |
| P13671 | Complement C6 | P0DJI8 | Serum amyloid A | P39900 | Matrix metalloproteinase 12/Macrophage metalloelastase |
| P10643 | Complement C7 | P02787 | Transferrin | P04085 | Platelet-derived growth factor A chain homodimer |
| P07357 | Complement C8 | P08887 | Interleukin-6 receptor alpha chain | P01127 | Platelet-derived growth factor B chain homodimer |
| P02748 | Complement C9 | P18428 | Lipopolysaccharide-binding protein | P00747 | Plasmin |
| P00751 | Complement factor B | Q9GZX6 | Interleukin-22 | P00747 | Plasminogen |
| P08603 | Complement factor H | Q14624 | Inter-alpha-trypsin inhibitor heavy chain H4 | P03952 | Prekallikrein |
| P01024 | Complement C3b, inactivated | Q86VB7 | Scavenger receptor cysteine-rich type 1 protein M130 chain/Soluble CD163 | P17252 | Protein kinase C alpha |
| P20809 | Interleukin-11 | P02751 | Fibronectin-1 Fragment 4 | P00734 | Prothrombin |
| P05112 | Interleukin-4 | P02751 | Fibronectin-1 Fragment 3 | P00734 | Thrombin |
| P16109 | P-Selectin |  |  | P03951 | Coagulation Factor XI |
| P02743 | Serum amyloid P |  |  | P07996 | Thrombospondin-1 |
| P22301 | Interleukin-10 |  |  | P02776 | Platelet factor 4 |
| P35225 | Interleukin-13 |  |  | P02679 | Fibrinogen gamma chain dimer |
| P16581 | E-Selectin |  |  | P29965 | CD40 ligand |
| O75636 | Ficolin-3 |  |  | Q08345 | Discoidin domain receptor 1 |
| P06681 | Complement C2 |  |  | Q02297 | Neuregulin-1 |
| Q13219 | Pregnancy-associated plasma protein-A |  |  | O15520 | Fibroblast growth factor 10/Keratinocyte growth factor 2 |
| P01024 | Complement C3a anaphylatoxin des Arginine |  |  | Q9NP84 | TWEAK receptor/TNFRSF12A |
| P00746 | Complement factor D |  |  | P00740 | Coagulation Factor IXab |
| P05156 | Complement factor I |  |  | P07093 | Protease nexin I |
| P01024 | Complement C3d |  |  | P17813 | Endoglin |
| Q15848 | Adiponectin |  |  | P02649 | Apolipoprotein E3 |
| P12956 | ATP-dependent DNA helicase II 70 kDa subunit |  |  | P02649 | Apolipoprotein E4 |
| P11226 | Mannose-binding protein C |  |  | P37023 | Activin receptor-like kinase 1 |
| P08174 | CD55/Complement decay-accelerating factor/DAF |  |  | O00299 | Nuclear chloride ion channel 27 |
| Q15485 | Ficolin-2 |  |  | Q9H2X3 | Dendritic cell-specific ICAM-3-grabbing nonintegrin 2/CD299 |
| P27658 | Collagen alpha-1(VIII) chain |  |  | P06396 | Gelsolin |
| Q07021 | Complement C1q subcomponent-binding protein, mitochondrial |  |  | P04196 | Histidine-proline-rich glycoprotein |
| Q6YHK3 | CD109 |  |  | P07359 | Platelet Glycoprotein Ib alpha |
| P48740 | Mannan-binding lectin serine peptidase 1 |  |  | Q8WWQ8 | Stabilin-2 |
|  |  |  |  | O00755 | Wingless-type MMTV integration site family, member 7A |
|  |  |  |  | P53582 | Methionine aminopeptidase 1 |
|  |  |  |  | P42680 | Tyrosine-protein kinase Tec |
|  |  |  |  | P01042 | Kininogen-1, HMW, Single chain |