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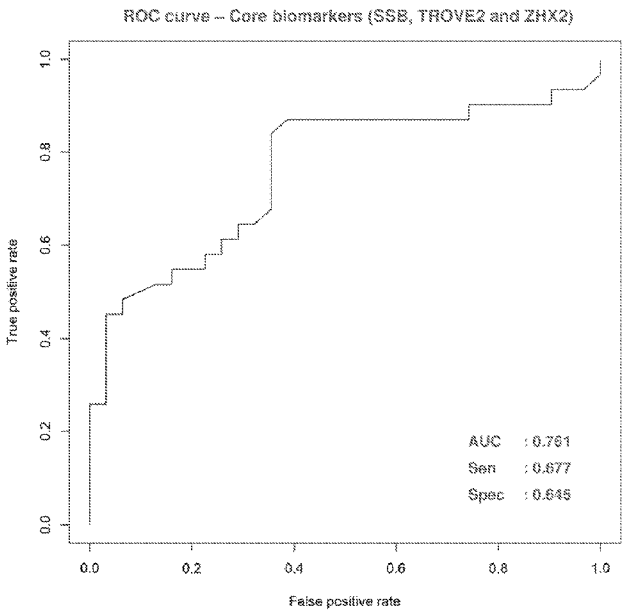
Figure 6



(57) Abstract: A method for predicting an immunogenic and/or therapeutic response to adalimumab 5 from a sample extracted from a rheumatoid arthritis patient by testing the sample for the presence of biomarkers, the biomarkers being autoantibodies to antigens comprising SSB, TROVE2 and ZHX2.

WO 2022/108522 A1

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BIOMARKERS FOR PREDICTING IMMUNOGENICITY AND THERAPEUTIC RESPONSES TO ADALIMUMAB IN RHEUMATOID ARTHRITIS PATIENTS

Field of Invention

The invention relates to the detection of immunological biomarkers, particularly autoantibodies, to predict immunogenicity and therapeutic responses to adalimumab in patients with Rheumatoid Arthritis (RA).

Background

Rheumatoid arthritis (RA), a chronic inflammatory articular disease, is characterized by persistent synovitis, cartilage degradation, and bone erosions [1], and tumor necrosis factor (TNF)-α is a crucial inflammatory mediator in RA-related synovitis and joint damage [2]. The importance of the role of TNF-α in RA pathogenesis is supported by the effectiveness of biologics targeting this cytokine [2-4], although the efficacy diminishes in some patients over time (secondary failure) [5]. Accumulating evidence indicates that the presence of anti-drug antibodies (ADAb) in certain patients may be associated with low or undetectable drug levels and ensuing reduction of therapeutic responsiveness to TNF-α inhibitors [6-10]. Such ADAb responses reflect the differential immunogenicity of the given biologic drug triggered in individual patients, which results in some patients developing a neutralising antibody response against the biologic drug and others not. In the face of such uncertainty about whether individual RA patients will show therapeutic responsiveness to TNF-α inhibitors or not [11], physicians hoping to optimize personalized and precision therapy are thus eager to find biomarkers which can predict the emergence of ADAb and the effectiveness of anti-TNF-α biologics.

Proteomics research has been increasingly applied to the identification of novel biomarkers that might be useful for monitoring therapeutic response in RA patients on specific treatments [12-14]. However, there is currently limited knowledge about circulating biomarkers that are able to predict the development of ADAb in RA patients receiving anti-TNF-α therapy.

Autoantibody biomarkers as described herein are autoantibodies to antigens, autoantibodies being antibodies which are produced by an individual which are directed against one or more of the individual's own proteins ('self' antigens).

The aim of the present invention therefore is to provide a novel panel of autoantibody biomarkers that are able to predict immunogenicity of adalimumab and therapeutic responses to adalimumab in individual RA patients, prior to treatment with adalimumab, a widely used TNF-α inhibitor marketed under the brand name HUMIRA® and commonly used for the treatment of autoimmune diseases, such as RA, Crohn's Disease and Psoriasis.

Summary of Invention

In one aspect of the invention, there is provided a method for predicting a response to adalimumab from a sample extracted from a rheumatoid arthritis patient prior to treating the patient with adalimumab, said response being classified as a good response corresponding to anti-drug antibody negative or a poor response corresponding to anti-drug antibody positive, comprising the steps of:

(i) testing the sample for the presence of autoantibody biomarkers; and

(ii) determining whether the patient will develop a good response or a bad response to treatment with adalimumab, based on the detection of said autoantibody biomarkers;

characterised in that the autoantibody biomarkers are autoantibodies to antigens comprising SSB, TROVE2 and ZHX2, wherein ZHX2 is associated with the good response, and SSB and TROVE2 are associated with the poor response.

Advantageously the autoantibody biomarkers can be used to predict immunogenicity of adalimumab and therapeutic responses to adalimumab in individual rheumatoid arthritis (RA) patients at baseline (i.e. prior to treating the patient with adalimumab).

In one embodiment the sample is tested using a panel of antigens that correspond to the autoantibody biomarkers. Typically the antigens are biotinylated proteins. Advantageously the biotinylation ensures that the antigens are folded in their correct form to ensure accuracy of detection by the autoantibody biomarkers.

In one embodiment the antigens may include one or more additional antigens from the group comprising of PPARD, SPANXN2, HNRNPA2B, TRIB2, CEP55, SH3GL1, FN3K, PANK3, HPCAL1, THRA, AIFM1, ODC1, RPS6KA4, EEF1D, KLF10, EPHA2, PRKAR1A and EAPP.

It should be noted that not all human antigens generate an autoantibody response and it is not possible to predict *a priori* which human antigens will do so in a given patient cohort – of the 1622 antigens tested, only autoantibodies against the 21 antigens described above are suitable as biomarkers in predicting immunogenicity of adalimumab and therapeutic responses to adalimumab in RA patient at baseline.

In one embodiment each biotinylated protein is formed from a Biotin Carboxyl Carrier Protein (BCCP) folding marker which is fused in-frame with the protein.

In one embodiment the biotinylated proteins are bound to a streptavidin-coated substrate.

Advantageously full-length proteins are expressed as fusions to the BCCP folding marker which itself becomes biotinylated *in vivo* when the fusion partner is correctly folded. By comparison misfolded fusion partners cause the BCCP to remain in the 'apo' (i.e. non-biotinylated) form such that it cannot attach to a streptavidin substrate. Thus only correctly folded fusion proteins become attached to the streptavidin substrate via the biotin moiety appended to the BCCP tag.

In one embodiment the substrate comprises a glass slide, biochip, strip, slide, bead, microtitre plate well, surface plasmon resonance support, microfluidic device, thin film polymer base layer, hydrogel-forming polymer base layer, or any other device or technology suitable for detection of antibody-antigen binding.

In one embodiment the substrate is exposed to a sample extracted from a person, such that autoantibody biomarkers from the sample may bind to the antigens.

Typically the sample comprises any or any combination of exosomes, blood, serum, plasma, urine, saliva, amniotic fluid, cerebrospinal fluid, breast milk, semen or bile.

Typically the sample is collected at baseline prior to administration of the first dose of adalimumab.

In one embodiment following exposure to the sample, the substrate is exposed to a fluorescently-tagged secondary antibody to allow the amount of any autoantibodies from the sample bound to the antigens on the panel to be determined. Typically the secondary antibody is anti-human IgG, but it will be appreciated that other secondary antibodies could be used, such as anti-IgM, anti-IgG1, anti-IgG2, anti-IgG3, anti-IgG4 or anti-IgA.

In one embodiment the patient's response to treatment with adalimumab (i.e. the immunogenic and/or therapeutic response outcome to adalimumab in RA patient at baseline) corresponds to the relative or absolute amount of autoantibodies from the baseline sample specifically binding to the antigens.

In one embodiment the method is performed *in vitro*.

In a further aspect of the invention, there is provided a method for manufacturing a kit for predicting a response to adalimumab from a sample extracted from a rheumatoid arthritis patient prior to treating the patient with adalimumab, comprising the steps of:

for each antigen in a panel, cloning a biotin carboxyl carrier protein folding marker in-frame with a gene encoding the antigen and expressing the resulting biotinylated antigen;

binding the biotinylated antigens to addressable locations on one or more streptavidin-coated substrates, thereby forming an antigen array;

such that the amount of autoantibodies from the sample binding to the antigens on the panel can be determined by exposing the substrate to the sample and measuring the immunogenicity and response;

characterised in that the antigens comprise SSB, TROVE2 and ZHX2.

In one embodiment the antigens further comprise one or more of PPARD, SPANXN2, HNRNPA2B, TRIB2, CEP55, SH3GL1, FN3K, PANK3, HPCAL1, THRA, AIFM1, ODC1, RPS6KA4, EEF1D, KLF10, EPHA2, PRKAR1A and EAPP.

In a further aspect of the invention there is provided a method for predicting immunogenicity of adalimumab and therapeutic responses to adalimumab in RA patients at baseline by exposing a composition comprising a panel of antigens as herein described to a sample extracted from a person, and determining the level of autoantibodies from the sample binding to the antigens.

In a yet further aspect of the invention there is provided a method for predicting immunogenicity of adalimumab and therapeutic responses to adalimumab in RA patients at baseline by exposing a composition comprising a panel of antigens as herein described to a sample extracted from a person *in vitro*, and determining the level of autoantibodies from the sample binding to the antigens.

In further aspect of the invention, there is provided a composition comprising a panel of antigens for predicting an immunogenic and/or therapeutic response to adalimumab in a rheumatoid arthritis patient who has not previously been treated with adalimumab, characterised in that the antigens comprise SSB, TROVE2 and ZHX2.

In one embodiment the antigens further comprise one or more of PPARD, SPANXN2, HNRNPA2B, TRIB2, CEP55, SH3GL1, FN3K, PANK3, HPCAL1, THRA, AIFM1, ODC1, RPS6KA4, EEF1D, KLF10, EPHA2, PRKAR1A and EAPP.

In one embodiment the antigens are biotinylated proteins

In one embodiment the amount of one or more autoantibody biomarkers binding *in vitro* to the antigens in a sample from a patient can be measured to determine the immunogenicity and therapeutic response outcome to adalimumab in an RA patient at baseline.

In yet further aspect of the invention, there is provided a composition comprising a panel of autoantibody biomarkers for predicting an immunogenic and/or therapeutic response to adalimumab in a rheumatoid arthritis patient who has not previously been treated with adalimumab, wherein the level of the autoantibody biomarkers are measured in a sample collected from the patient;

characterised in that the autoantibody biomarkers are specific to antigens comprising SSB, TROVE2 and ZHX2.

Brief Description of Drawings

It will be convenient to further describe the present invention with respect to the accompanying drawings that illustrate possible arrangements of the invention. Other arrangements of the invention are possible, and consequently the particularity of the accompanying drawings is not to be understood as superseding the generality of the preceding description of the invention.

Figure 1 illustrates the structure of the *E. coli* Biotin Carboxyl Carrier Protein domain.

Figure 2 illustrates the pPRO9 plasmid used as a vector.

Figure 3 illustrates the distribution of the normalised RFU (i.e. autoantibody responses) for all 21 biomarkers between ADAb-positive (Group A) and ADAb-negative (Group B) RA patients collected at baseline.

Figure 4 illustrates the discriminatory performance represented as a receiver operating curve (ROC) with an area under the curve (AUC) of 0.835 for all 21 biomarkers (SSB, TROVE2, ZHX2, PPARD, SPANXN2, HNRNPA2B, TRIB2, CEP55, SH3GL1, FN3K, PANK3, HPCAL1, THRA, AIFM1, ODC1, RPS6KA4, EEF1D, KLF10, EPHA2, PRKAR1A and EAPP) between ADAb-positive (Group A) and ADAb-negative (Group B) RA patients collected at baseline.

Figure 5 illustrates the variable importance measure for each of the 21 biomarkers identified in the study.

Figure 6 illustrates the discriminatory performance represented as a receiver operating curve (ROC) with an area under the curve (AUC) of 0.761 for the core biomarkers (SSB, TROVE2 and ZHX2) between ADAb-positive (Group A) and ADAb-negative (Group B) RA patients collected at baseline.

Detailed Description

The invention utilises the Biotin Carboxyl Carrier Protein (BCCP) folding marker which is cloned in-frame with the gene encoding the protein of interest, as described above and in EP1470229. The structure of the *E. coli* BCCP domain is illustrated in Figure 1, wherein residues 77-156 are drawn (coordinate file 1bdo) showing the N- and C- termini and the single biotin moiety that is attached to lysine-122 *in vivo* by biotin ligase.

BCCP acts not only as a protein folding marker but also as a protein solubility enhancer. BCCP can be fused to either the N- or C-terminal of a protein of interest. Full-length proteins are expressed as fusions to the BCCP folding marker which becomes biotinylated *in vivo*, but only when the protein is correctly folded. Conversely, misfolded proteins drive the misfolding of BCCP such that it is unable to become biotinylated by host biotin ligases. Hence, misfolded proteins are unable to specifically attach to a streptavidin-coated solid support. Therefore only correctly folded proteins become attached to a solid support via the BCCP tag.

The surface chemistry of the support is designed carefully and may use a three-dimensional thin film hydrogel layer (polyethylene glycol; PEG), which retains protein spot morphologies and ensures consistent spot sizes across the array. The PEG layer inhibits non-specific macromolecule absorption, therefore reducing the high background observed using other platforms. The solid support used to immobilize the selected biomarkers thus provides excellent signal-to-noise ratios and low limits of detection (translating in to improved sensitivity). In addition the PEG hydrogel layer also aids preservation of the folded structure and functionality of arrayed proteins and protein complexes post-immobilisation.

Retention of the correct folded structure of immobilised antigens during antibody binding assays ('immuno-assays') is particularly advantageous because human antibodies are

known in general to specifically recognise and bind to discontinuous, solvent-accessible epitopes on protein surfaces, yet are also known to bind non-specifically to exposed hydrophobic surfaces on unfolded proteins. Thus serological assays carried out on arrays of unfolded proteins typically give rise to many false positive results due to such non-specific binding events (which have no biological relevance), whilst at the same time also giving rise to many false negative results due to the absence of biologically-relevant discontinuous epitopes. By contrast, serological assays carried out on arrays of folded antigens result in detection of biologically meaningful antibody-antigen interactions that are not obscured by high rates of non-specific binding.

As biotinylated proteins bound to a streptavidin-coated surface show negligible dissociation, this interaction therefore provides a superior means for tethering proteins to a planar surface in a controlled orientation and is thus ideal for applications such as protein arrays, SPR and bead-based assays. The use of a compact, folded, biotinylated, 80 residue domain BCCP affords two significant advantages over for example the AviTag and intein-based tag. First, the BCCP domain is cross-recognised by eukaryotic biotin ligases enabling it to be biotinylated efficiently in yeast, insect, and mammalian cells without the need to co-express the *E. coli* biotin ligase. Second, the N- and C-termini of BCCP are physically separated from the site of biotinylation by 50Å (as shown in Figure 1), so the BCCP domain can be thought of as a stalk which presents the recombinant proteins away from the solid support surface, thus minimising any deleterious effects due to immobilisation.

The addition of BCCP permits the monitoring of fusion protein folding by measuring the extent of *in vivo* biotinylation. This can be measured by standard blotting procedures, using SDS-PAGE or *in situ* colony lysis and transfer of samples to a membrane, followed by detection of biotinylated proteins using a streptavidin conjugate such as streptavidin-horseradish peroxidase. Additionally, the fact that the BCCP domain is biotinylated *in vivo* is particularly useful when multiplexing protein purification for fabrication of protein arrays since the proteins can be simultaneously purified from cellular lysates and immobilised in a single step via the high affinity and specificity exhibited by a streptavidin surface.

Example 1

Materials and Methods

Gene synthesis and cloning. The pPRO9 plasmid (see Figure 2 below) was constructed by standard techniques and consists of genetic elements encoding a c-myc tag and a BCCP protein domain, preceded by a multiple-cloning site. Synthetic genes encoding individual human antigens were assembled from synthetic oligonucleotides and were cloned into pPRO9 using *Spe*I and *Nco*I cloning sites such that each resultant clonal 'transfer vector' encoded an in-frame fusion protein comprising a specific human antigen fused to the BCCP tag. The plasmid DNA was purified from transformed bacteria and verified by DNA sequencing. The required sequence congruence within the synthetic gene region was 100%.

Recombinant baculovirus was generated via co-transfection of Sf9 cells (a clonal isolate derived from the parental *Spodoptera frugiperda* cell line IPLB-Sf-21-AE) with a replication-deficient bacmid vector carrying the viral polyhedrin promoter and a transfer vector carrying a specific coding sequence for a specific antigen. Homologous recombination between the transfer vector and the bacmid within Sf9 cells resulted in formation of a replication competent baculoviral vector encoding the specific antigen fused to the BCCP tag. Successful homologous recombination between the transfer vector and the bacmid within Sf9 cells caused the transfected cells to show signs of viral cytopathic effect (CPE) within few days of culture incubation. The most common CPE observed was the significantly enlargement of average cell size, a consequences of viral progeny propagation. These baculoviruses known as P0 were then released into the culture medium, and viral amplification were done to generate a higher titre of P1 viruses.

Protein Expression. Expression of recombinant antigens was carried out in 24 well blocks using 3ml cultures containing $6x10^6$ Sf9 cells per well. High titre, low passage, viral stocks of recombinant baculovirus ($>10^7$ pfu/ml) were used to infect Sf9 insect cells. The infected cells were then cultured for 72 hours to allow them to produce the recombinant protein of interest. The cells were washed with PBS, resuspended in buffer, and were frozen in aliquots at -80°C ready for lysis as required. Depending on the transfer vector construct and the nature of the antigen itself, the resultant recombinant protein

lysate can be recovered either from the cultured cell or the culture medium. Expression of recombinant proteins was confirmed by SDS-PAGE as well as by Western blot using streptavidin-HRP-based detection. In total, 1622 human antigens were cloned and expressed using this methodology.

Array fabrication. Hydrogel coated, streptavidin-derivatised slides were custom manufactured by Schott and used as substrates on to which the biotinylated proteins were then printed. A total of 9 nanoliters of crude protein lysate was printed on a HS slide in quadruplicate using non-contact piezo printing technology. Print buffer that have a pH between 7.0 and 7.5 were used. The slides were dried by centrifugation (200 x g for 5 min) before starting the washing and blocking. The printed arrays were blocked with solutions containing BSA or casein (concentration: 0.1 mg/ml) in a phosphate buffer. The pH was adjusted to be between 7.0 and 7.5 and cold solutions were used (4 °C - 20 °C). Slides were not allowed to dry between washes, and were protected from light. In total, each resultant 'Immunome array' comprised 1622 antigens, each printed in quadruplicate.

Experimental Procedure.

1. Study cohort

The study cohort comprised of a total of 62 plasma and serum samples collected from RA patients at baseline (i.e. prior to treatment administration);

i. Run 1: 6 ADAb-positive ("poor response") and 6 ADAb-negative ("good response")
ii. Run 2: 24 ADAb-positive ("poor response") and 26 ADAb-negative ("good response")

Patients were administered with *adalimumab* at a dose of 40mg every other week. The immunogenicity and therapeutic response to *adalimumab* were evaluated at week 24, the latter by using the EULAR response criteria [15]. EULAR responders were defined as RA patients with good and moderate ("good response") or poor ("poor response") EULAR therapeutic responses.

2. Sample Collection and Storage

Peripheral blood samples were collected immediately before the first adalimumab administration (the baseline sample) and also at week 24. After centrifugation at 1000 g for 10 min within 15 min of withdrawal, serum and plasma samples were stored at -70°C.

3. Sample Preparation and Dilution

For each run, samples were placed in a shaking incubator set at 20°C to allow thawing for 30 minutes. When completely thawed, each sample was vortexed vigorously three times and debris was pelleted by centrifugation for 3 minutes at 13,000 rpm. 11.25 µL of the sample was pipetted into 4.5 mL of Serum Assay Buffer (SAB) containing 0.1% v/v Triton, 0.1% w/v BSA in PBS (20°C) and vortexed to mix three times. The tube was tilted during aspiration to ensure that the sera was sampled from below the lipid layer at the top but did not touch the bottom of the tube in case of presence of any sediment. Batch records were marked accordingly to ensure that the correct samples were added to the correct tubes. Samples were then randomised prior to assay.

4. Biomarker Assay

Each Immunome array was removed from the storage buffer using forceps, placed in the slide box and rack containing 200 mL cold SAB and shaken on an orbital shaker at 50 rpm, for 5 minutes. After washing, each slide was scanned using a barcode scanner and then placed array side up in an individual slide hybridization chamber containing an individual diluted sera (Step 3 above). All slides were and incubated on a horizontal shaker at 50 rpm for 2 hours at 20°C.

5. Array Washing After Serum Binding

Each Immunome array slide was rinsed twice in individual “Pap jars” with 30 mL SAB, followed by 200 mL of SAB buffer in the slide staining box for 20 minutes on the shaker at 50 rpm at room temperature. All slides were transferred sequentially and in the same orientation.

6. Incubation with Cy3-anti-human IgG

Binding of autoantibodies to the arrayed antigens on the arrays was detected by incubation with Cy3-rabbit anti-human IgG (Dako Cytomation) labelled according to the manufacturer's recommended protocols (GE Healthcare). Arrays were immersed in

hybridization solution containing a mixture of Cy3- rabbit anti-human IgG solution diluted 1:1000 in SAB buffer for 2 hours at 50 rpm in 20°C.

7. Washing After Incubation with Cy3-anti-human IgG

After incubation, the slide was dipped in 200 mL of SAB buffer, 3 times for 5 minutes at 50 rpm at room temperature. Excess buffer was removed by immersing the slide in 200 mL of pure water for a few minutes. Slides were then dried for 2 min by centrifugation at 240g at room temperature. Slides were then stored at room temperature until scanning. Fluorescent hybridization signals were measured with excitation at 550nm and emission at 570nm using a microarray laser scanner (Agilent) at 10μm resolution.

Bioinformatic analysis.

1. Image Analysis: Raw Data Extraction

The aim of an image analysis is to evaluate the amount of autoantibody present in the serum sample by measuring the median intensities of all the pixels within each probed spot. A raw .tiff format image file is generated for each slide, i.e. each sample. Automatic extraction and quantification of each spot on the array are performed using the GenePix Pro 7 software (*Molecular Devices*) which outputs the statistics for each probed spot on the array. This includes the mean and median of the pixel intensities within a spot as well as in its surrounding local background area. A GAL (GenePix Array List) file for the array is generated to enable image analysis. This file contains the information of all probed spots and their positions on the array. Following data extraction, a GenePix Results (.GPR) file is generated for each slide which contains the information for each spot: Protein ID, protein name, foreground intensities, background intensities etc. In the data sheet generated from the experiment, both foreground and background intensities of each spot are represented in relative fluorescence units (RFUs).

2. Data Handling and Pre-processing

For each slide, antigens and control probes are spotted in quadruplicate on each array. The following steps were performed to verify the quality of the antigen array data before proceeding with data analysis:

Step 1:

Calculate net intensities for each spot by subtracting background signal intensities from the foreground signal intensities of each spot. For each spot, the background signal intensity was calculated using a circular region with three times the diameter of the spot, centered on the spot.

Step 2:

Remove replica spots with net intensity ≤ 0.

Step 3:

Zero net intensities if only 1 replica spot remaining.

Step 4:

Calculate the coefficient of variant (CV%) for the replica spots on each array.

$$\mathrm{CV\%} = \frac{\mathrm{S.D.}}{\mathrm{Mean}} \times 100\% \qquad \textbf{Equation 1}$$

Flag any replica spots with only 2 or less replica/s remaining and CV% > 20% as "High CV". The mean net intensity of such replica spots (i.e. antigens) is excluded from downstream analysis.

For antigens/controls with a CV% > 20% and with 3 or more replica spots remaining, the replica spots which result in this high CV% value were filtered out. This was done by calculating the standard deviation between the median value of the net intensities and individual net intensities for each set of replica spots. The spot with the highest standard deviation was removed. CV% values were re-calculated and the process repeated.

Step 5:

Calculate the mean of the net intensities for the remaining replica spots.

Step 6:

Inspect signal intensities of two positive controls: IgG and Cy3-BSA.

Step 7:

Carry out a composite normalisation [16] using both quantile-based and total intensity-based modules for each dataset . This method assumes that different samples share a common underlying distribution of their control probes while taking into account the potential existence of flagged spots within them. The Immunome array uses Cy3-labelled biotinylated BSA (Cy3-BSA) replicates as the positive control spots across slides. Hence it is considered as a 'housekeeping' probe for normalisation of signal intensities for any given study.

The quantile module adopts the algorithm described by Bolstad *et al.*, 2003 [17]. This reorganisation enables the detection and handling of outliers or flagged spots in any of the Cy3BSA control probes. A total intensity-based module was then implemented to obtain a scaling factor for each sample. This method assumes that post-normalisation, the positive controls should have a common total intensity value across all samples. This composite method aims to normalise the protein array data from variations in their measurements whilst preserving the targeted biological activity across samples. The steps are as follows:

Quantile-Based Normalisation of all cy3BSA across all samples

($i = spot\ number\ and\ j = sample\ number$)

1. Load all Cy3-BSA across all samples, j, into an i X j matrix X
2. Sort spot intensities in each column j of X to get X_{sort}
3. Take the mean across each row i of X_{sort} to get $< X_i >$

Intensity-Based Normalisation

1. Calculate sum of the mean across each row i , $\sum < Xi >$
2. For each sample, k, calculate the sum of all Cy3-BSA controls, $\sum Xk$
3. For each sample, k,

$$\text{Scaling factor (k)} = \frac{\sum < \text{Xi} >}{\sum \text{Xk}} \qquad \textbf{Equation 2}$$

3. Data Analysis

Batch normalisation: The composite normalised data sets from the assays in the two runs were merged using a ComBat normalisation method [18]. For each protein, this method inputs the net intensity values across all the samples from the 2 data sets and adjusts for any possible batch effects between the two data sets using a parametric empirical Bayes frameworks.

Biomarker Panel Selection: A pipeline was developed which utilises a combination of feature selection and machine learning methodologies to determine the optimal combination of antigens eliciting autoantibody responses from the list of 1622 antigens which are able to provide the best stratification between ADAb-positive and ADAb-negative patients [19]. For feature selection, univariate statistical tests, random forest importance and mutual information metrics were the filter methods used to rank biomarkers.

Biomarker panels were generated by additively selecting the top-ranking biomarkers as inputs to machine learning models up to a total of top 160 biomarkers (top 10% of biomarkers). Any further addition of number of biomarkers did not lead to significant improvements of model performance and would lead to further increase of computational time. To estimate the biomarker panel performance, ROC, sensitivity and specificity was evaluated and the biomarker panel with the best sensitivity and specificity was deemed as the optimal panel to stratify ADAb status. For this analysis, machine learning models were built using Random Forests [20], under default settings with leave-one out cross validation (LOOCV). All analyses were performed using packages available in R. Feature selection was performed using ranger [21] package and all machine learning models were performed using the caret [22] package.

Table 1 shows top 4 best performing biomarker panel from the machine learning models using leave-one out cross validation. The lowest number of antigens with the highest sensitivity and specificity was deemed to be the top biomarker panel. This panel comprises SSB, TROVE2, ZHX2, PPARD, SPANXN2, HNRNPA2B, TRIB2, CEP55, SH3GL1, FN3K, PANK3, HPCAL1, THRA, AIFM1, ODC1, RPS6KA4, EEF1D, KLF10, EPHA2, PRKAR1A and EAPP. Figure 3 shows the distribution of the normalised net intensity (i.e. autoantibody responses) for each of these 21 individual biomarkers in

ADAb-positive (Group A) and ADAb-negative (Group B) RA patients at baseline. Figure 4 shows the discriminatory performance of the combined panel of 21 autoantibody biomarkers represented as a receiver operating curve (ROC), yielding an area under the curve (AUC) of 0.835.

The biomarkers were ranked based on Random Forests estimated variable importance measure [23] derived from each panel (Figure 5 and Table 2). This further identified a core set of biomarkers which are common across the top 4 biomarker panels, comprising SSB, TROVE2 and ZHX2, with an AUC performance of 0.761 (Figure 6).

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cluster-analysis based protein score. *Scand J Rheumatol* 2018;**47**:12-21.

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Table 1

test	No of antigen	Biomarkers in panel	ROC	Sens	Spec
ranger_permutation	20	SSB,TROVE2,ZHX2,PPARD,SPANXN2,HNRNPA2B1,TRIB2,CEP55,SH3GL1,FN3K,PANK3,HPCAL1,THRA,AIFM1,ODC1,RPS6KA4,EEF1D,KLF10,EPHA2,PRKAR1A	0.821	0.806	0.774
ranger_permutation	21	SSB,TROVE2,ZHX2,PPARD,SPANXN2,HNRNPA2B1,TRIB2,CEP55,SH3GL1,FN3K,PANK3,HPCAL1,THRA,AIFM1,ODC1,RPS6KA4,EEF1D,KLF10,EPHA2,PRKAR1A,EAPP	0.835	0.839	0.774
ranger_permutation	28	SSB,TROVE2,ZHX2,PPARD,SPANXN2,HNRNPA2B1,TRIB2,CEP55,SH3GL1,FN3K,PANK3,HPCAL1,THRA,AIFM1,ODC1,RPS6KA4,EEF1D,KLF10,EPHA2,PRKAR1A,EAPP,ZNF331,GMPS,POTEE,ASPSCR1,ECI2,ETV7,BUD31	0.824	0.839	0.710
ranger_permutation	29	SSB,TROVE2,ZHX2,PPARD,SPANXN2,HNRNPA2B1,TRIB2,CEP55,SH3GL1,FN3K,PANK3,HPCAL1,THRA,AIFM1,ODC1,RPS6KA4,EEF1D,KLF10,EPHA2,PRKAR1A,EAPP,ZNF331,GMPS,POTEE,ASPSCR1,ECI2,ETV7,BUD31,ATF3	0.811	0.839	0.774

Table 2

test	Importance value	Ranking
SSB	0.003172	1
TROVE2	0.003142	2
ZHX2	0.002135	3
PPARD	0.001290	4
SPANXN2	0.000886	5
HNRNPA2B1	0.000870	6
TRIB2	0.000825	7
CEP55	0.000814	8
SH3GL1	0.000776	9
FN3K	0.000759	10
PANK3	0.000703	11
HPCAL1	0.000689	12
THRA	0.000657	13
AIFM1	0.000639	14
ODC1	0.000638	15
RPS6KA4	0.000613	16
EEF1D	0.000590	17
KLF10	0.000588	18
EPHA2	0.000587	19
PRKAR1A	0.000587	20
EAPP	0.000565	21

Table 3

Protein Name	UniprotID	Description
SSB	P05455	Lupus La protein

Nucleotide Sequence **(Seq ID No. 1)***:*
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FVVFDSIESAKKFVETPGQKYKETDLLILFKDDYFAKKNEERKQNKVEAKLRAKQEQEAKQKLEEDAEMKSLEEKI
GCLLKFSGDLDDQTCREDLHILFSNHGEIKWIDFVRGAKEGIILFKEKAKEALGKAKDANNGNLQLRNKEVTWEVL
EGEVEKEALKKIIEDQQESLNKWKSKGRRFKGKGKGNKAAQPGSGKGKVQFQGKKTKFASDDEHDEHDENGAT
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TROVE2	P10155	HUMAN 60 kDa SS-A/Ro ribonucleoprotein

Nucleotide Sequence **(Seq ID No. 2)***:*
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ZHX2 Q9Y6X8 Zinc fingers and homeoboxes protein 2

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Protein Sequence **(Seq ID No. 24)***:*
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PPARD Q03181 Peroxisome proliferator-activated receptor delta

Nucleotide Sequence **(Seq ID No. 4)***:*
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SPANXN2 Q5MJ10 Sperm protein associated with the nucleus on the X chromosome N2

Nucleotide Sequence **(Seq ID No. 5)***:*
>P003098_Q211_Q211_tube_SPANXN2_494119_0_NM_001009615.1_0_Q5MJ10_0_Insert sequence is gene optimized by GeneArt_0_0_0

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Protein Sequence **(Seq ID No. 26)***:*
>sp|Q5MJ10|SPXN2_HUMAN Sperm protein associated with the nucleus on the X chromosome N2 OS=Homo sapiens OX=9606 GN=SPANXN2 PE=1 SV=1

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NSINPVQEEEDEGLDSAEGSSQEDEDLDSSEGSSQEDEDLDSSEGSSQEDEDLDSSEGSSQEDEDLDSSEGSS
QEDEDLDPPEGSSQEDEDLDSSEGSSQEGGED

HNRNPA2B1 P22626 Heterogeneous nuclear ribonucleoproteins A2/B1

Nucleotide Sequence **(Seq ID No. 6)***:*
>P003186_Q311_Q311_tube_HNRNPA2B1_3181_0_NM_002137.3_0_P22626_0

ATGGAACGCGAGAAAGAGCAGTTCCGCAAGCTGTTCATCGGTGGCCTGTCCTTCGAGACTACCGAGGAATC
CCTGCGCAACTACTACGAGCAGTGGGGCAAGCTGACCGACTGCGTGGTCATGCGTGACCCCGCTTCCAAG
CGTTCCCGTGGTTTCGGTTTCGTGACCTTCTCCAGCATGGCTGAGGTGGACGCTGCTATGGCTGCTCGTCC
CCACTCCATCGACGGTCGTGTGGTCGAGCCTAAGCGTGCTGTGGCTCGTGAAGAGTCCGGCAAGCCTGGT
GCTCACGTGACCGTGAAGAAGCTGTTCGTTGGCGGTATCAAAGAGGACACCGAGGAACACCACCTGAGGG
ACTACTTCGAGGAATACGGCAAGATCGACACCATCGAGATCATCACCGACCGTCAGTCCGGAAAGAAGCGC
GGCTTCGGCTTCGTCACTTTCGACGACCACGACCCCGTGGACAAGATCGTGCTGCAGAAGTACCACACCAT
CAACGGTCACAACGCTGAAGTGCGCAAGGCTCTGTCCCGTCAAGAGATGCAAGAGGTGCAGTCCTCCCGTT
CCGGTCGTGGTGGCAACTTCGGATTCGGCGACTCTCGCGGTGGTGGCGGAAACTTCGGTCCTGGTCCCGG
TTCCAACTTCCGTGGTGGTTCCGACGGTTACGGCTCCGGAAGAGGTTTCGGCGACGGCTACAACGGCTAC
GGTGGTGGTCCTGGCGGTGGAAATTTCGGTGGTTCCCCTGGTTACGGTGGCGGTCGCGGTGGATACGGCG
GAGGTGGTCCAGGATACGGCAACCAGGGTGGCGGTTACGGCGGTGGTTACGACAACTACGGTGGCGGCA
ACTACGGTTCCGGAAACTACAACGACTTCGGCAATTACAACCAGCAGCCCTCCAACTACGGCCCCATGAAG
TCTGGCAATTTCGGCGGCTCCCGTAACATGGGTGGTCCTTACGGTGGTGGAAATTACGGTCCCGGTGGTTC
CGGTGGCTCTGGTGGCTACGGCGGTCGTTCCCGTTAC

Protein Sequence **(Seq ID No. 27)***:*
>sp|P22626|ROA2_HUMAN Heterogeneous nuclear ribonucleoproteins A2/B1 OS=Homo sapiens OX=9606 GN=HNRNPA2B1 PE=1 SV=2

MEKTLETVPLERKKREKEQFRKLFIGGLSFETTEESLRNYYEQWGKLTDCVVMRDPASKRSRGFGFVTFSSMAE
VDAAMAARPHSIDGRVVEPKRAVAREESGKPGAHVTVKKLFVGGIKEDTEEHHLRDYFEEYGKIDTIEIITDRQSG
KKRGFGFVTFDDHDPVDKIVLQKYHTINGHNAEVRKALSRQEMQEVQSSRSGRGGNFGFGDSRGGGGNFGPG
PGSNFRGGSDGYGSGRGFGDGYNGYGGGPGGGNFGGSPGYGGGRGGYGGGGPGYGNQGGGYGGGYDNY
GGGNYGSGNYNDFGNYNQQPSNYGPMKSGNFGGSRNMGGPYGGGNYGPGGSGGSGGYGGRSRY

TRIB2 Q92519 HUMAN Tribbles homolog 2

Nucleotide Sequence **(Seq ID No. 7)***:*
>P001066_KIN2_KIN2p1_TRB2_28951_Homo sapiens tribbles homolog 2_BC002637.2_AAH02637.1_Q92519_0_0_1032_0_1029

ATGAACATACACAGGTCTACCCCCATCACAATAGCGAGATATGGGAGATCGCGGAACAAAACCCAGGATTT
CGAAGAGTTGTCGTCTATAAGGTCCGCGGAGCCCAGCCAGAGTTTCAGCCCGAACCTCGGCTCCCCGAGC
CCGCCCGAGACTCCGAACTTGTCGCATTGCGTTTCTTGTATCGGGAAATACTTATTGTTGGAACCTCTGGAG
GGAGACCACGTTTTTCGTGCCGTGCATCTGCACAGCGGAGAGGAGCTGGTGTGCAAGGTGTTTGATATCAG
CTGCTACCAGGAATCCCTGGCACCGTGCTTTTGCCTGTCTGCTCATAGTAACATCAACCAAATCACTGAAAT
TATCCTGGGTGAGACCAAAGCCTATGTGTTCTTTGAGCGAAGCTATGGGGACATGCATTCCTTCGTCCGCAC
CTGCAAGAAGCTGAGAGAGGAGGAGGCAGCCAGACTGTTCTACCAGATTGCCTCGGCAGTGGCCCACTGC
CATGACGGGGGGCTGGTGCTGCGGGACCTCAAGCTGCGGAAATTCATCTTTAAGGACGAAGAGAGGACTC
GGGTCAAGCTGGAAAGCCTGGAAGACGCCTACATTCTGCGGGGAGATGATGATTCCCTCTCCGACAAGCAT
GGCTGCCCGGCTTACGTAAGCCCAGAGATCTTGAACACCAGTGGCAGCTACTCGGGCAAAGCAGCCGACG
TGTGGAGCCTGGGGGTGATGCTGTACACCATGTTGGTGGGGCGGTACCCTTTCCATGACATTGAACCCAGC
TCCCTCTTCAGCAAGATCCGGCGTGGCCAGTTCAACATTCCAGAGACTCTGTCGCCCAAGGCCAAGTGCCT
CATCCGAAGCATTCTGCGTCGGGAGCCCTCAGAGCGGCTGACCTCGCAGGAAATTCTGGACCATCCTTGGT
TTTCTACAGATTTTAGCGTCTCGAATTCAGCATATGGTGCTAAGGAAGTGTCTGACCAGCTGGTGCCGGACG
TCAACATGGAAGAGAACTTGGACCCTTTCTTTAAC

Protein Sequence **(Seq ID No. 28)***:*
>splQ92519lTRIB2_HUMAN Tribbles homolog 2 OS=Homo sapiens OX=9606 GN=TRIB2 PE=1 SV=1

MNIHRSTPITIARYGRSRNKTQDFEELSSIRSAEPSQSFSPNLGSPSPPETPNLSHCVSCIGKYLLLEPLEGDHVFR
AVHLHSGEELVCKVFDISCYQESLAPCFCLSAHSNINQITEIILGETKAYVFFERSYGDMHSFVRTCKKLREEEAAR
LFYQIASAVAHCHDGGLVLRDLKLRKFIFKDEERTRVKLESLEDAYILRGDDDSLSDKHGCPAYVSPEILNTSGSY
SGKAADVWSLGVMLYTMLVGRYPFHDIEPSSLFSKIRRGQFNIPETLSPKAKCLIRSILRREPSERLTSQEILDHPW
FSTDFSVSNSAYGAKEVSDQLVPDVNMEENLDPFFN

CEP55 Q53EZ4 Centrosomal protein of 55 kDa

Nucleotide Sequence **(Seq ID No. 8)***:*
>P003121_Q211_Q211_tube_CEP55_55165_0_NM_001127182.1_0_Q53EZ4_0

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GACTACCCTCGAGAAGCTGAAGGGCGAGATCGCTCACCTCAAGACCTCCGTGGACGAGATCACCTCCGGC
AAGGGCAAGCTGACCGACAAGGAACGTCACCGTCTGCTCGAGAAGATCCGTGTGCTCGAGGCTGAGAAGG
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GCTGGAATCCAAGACCAACACCCTGCGTCTGTCCCAGACCGTGGCTCCCAACTGCTTCAACTCCTCCATCA
ACAACATCCACGAGATGGAAATCCAACTGAAGGACGCTCTCGAGAAGAACCAGCAGTGGCTGGTGTACGAC
CAGCAGCGCGAGGTGTACGTGAAGGGCCTGCTGGCTAAGATCTTCGAGCTGGAAAAGAAGACCGAGACTG
CTGCTCACTCCCTGCCCCAGCAGACCAAGAAGCCCGAGTCCGAGGGTTACCTGCAAGAGGAAAAGCAGAA
GTGCTACAACGACCTGCTGGCTTCCGCTAAGAAGGACCTGGAAGTCGAGCGTCAGACCATCACCCAGCTGT
CCTTCGAGCTGTCCGAGTTCCGTAGGAAGTACGAAGAGACTCAGAAGGAAGTCCACAACCTGAACCAGCTG
CTGTACTCCCAGCGTCGTGCTGACGTGCAGCACCTCGAGGACGACCGTCACAAGACTGAGAAGATCCAGA
AGCTGCGCGAAGAGAACGATATCGCTCGTGGCAAGCTCGAGGAAGAGAAGAAGCGTTCCGAGGAACTGCT
GTCCCAGGTGCAGTTCCTGTACACCTCCCTGCTCAAGCAGCAAGAGGAACAGACCCGTGTGGCTCTGTTGG
AGCAGCAGATGCAGGCTTGCACCCTGGACTTCGAGAACGAGAAGCTGGACCGTCAGCACGTCCAGCACCA
GCTGCACGTGATCCTGAAGGAACTGCGCAAGGCTCGTAACCAGATCACCCAGTTGGAGTCCCTGAAGCAG
CTGCACGAGTTCGCTATCACCGAGCCCCTGGTCACCTTCCAAGGCGAGACTGAGAACCGCGAGAAGGTGG
CCGCTTCCCCCAAGTCCCCCACCGCTGCTCTGAACGAGTCCCTGGTCGAGTGCCCCAAGTGCAACATCCA
GTACCCCGCTACCGAGCACCGTGACCTGCTGGTGCACGTCGAGTACTGCTCCAAG

Protein Sequence **(Seq ID No. 29)***:*
>sp|Q53EZ4|CEP55_HUMAN Centrosomal protein of 55 kDa OS=Homo sapiens OX=9606 GN=CEP55 PE=1 SV=3

MSSRSTKDLIKSKWGSKPSNSKSETTLEKLKGEIAHLKTSVDEITSGKGKLTDKERHRLLEKIRVLEAEKEKNAYQ
LTEKDKEIQRLRDQLKARYSTTTLLEQLEETTREGERREQVLKALSEEKDVLKQQLSAATSRIAELESKTNTLRLS
QTVAPNCFNSSINNIHEMEIQLKDALEKNQQWLVYDQQREVYVKGLLAKIFELEKKTETAAHSLPQQTKKPESEG
YLQEEKQKCYNDLLASAKKDLEVERQTITQLSFELSEFRRKYEETQKEVHNLNQLLYSQRRADVQHLEDDRHKT
EKIQKLREENDIARGKLEEEKKRSEELLSQVQFLYTSLLKQQEEQTRVALLEQQMQACTLDFENEKLDRQHVQH
QLHVILKELRKARNQITQLESLKQLHEFAITEPLVTFQGETENREKVAASPKSPTAALNESLVECPKCNIQYPATEH
RDLLVHVEYCSK

SH3GL1 Q99961 Endophilin-A2

Nucleotide Sequence **(Seq ID No. 9)***:*
>P000121_CAN_CAN1-1_SH3GL1_6455_Homo sapiens SH3-domain GRB2-like 1_BC001270.1_AAH01270.1_Q99961_0_0_1107_0_1104

ATGTCGGTGGCGGGGCTGAAGAAGCAGTTCTACAAGGCGAGCCAGCTGGTCAGTGAGAAGGTCGGAGGG
GCCGAGGGGACCAAGCTGGATGATGACTTCAAAGAGATGGAGAAGAAGGTGGATGTCACCAGCAAGGCGG
TGACAGAAGTGCTGGCCAGGACCATCGAGTACCTGCAGCCCAACCCAGCCTCGCGGGCTAAGCTGACCAT
GCTCAACACGGTGTCCAAGATCCGGGGCCAGGTGAAGAACCCCGGCTACCCGCAGTCGGAGGGGCTTCTG
GGCGAGTGCATGATCCGCCACGGGAAGGAGCTGGGCGGCGAGTCCAACTTTGGTGACGCATTGCTGGATG
CCGGCGAGTCCATGAAGCGCCTGGCAGAGGTGAAGGACTCCCTGGACATCGAGGTCAAGCAGAACTTCAT
TGACCCCCTCCAGAACCTGTGCGAGAAAGACCTGAAGGAGATCCAGCACCACCTGAAGAAACTGGAGGGC
CGCCGCCTGGACTTTGACTACAAGAAGAAGCGGCAGGGCAAGATCCCCGATGAGGAGCTACGCCAGGCGC
TGGAGAAGTTCGAGGAGTCCAAGGAGGTGGCAGAAACCAGCATGCACAACCTCCTGGAGACTGACATCGA
GCAGGTGAGTCAGCTCTCGGCCCTGGTGGATGCACAGCTGGACTACCACCGGCAGGCCGTGCAGATCCTG
GACGAGCTGGCGGAGAAGCTCAAGCGCAGGATGCGGGAAGCTTCCTCACGCCCTAAGCGGGAGTATAAGC
CGAAGCCCCGGGAGCCCTTTGACCTTGGAGAGCCTGAGCAGTCCAACGGGGGCTTCCCCTGCACCACAGC
CCCCAAGATCGCAGCTTCATCGTCTTTCCGATCTTCCGACAAGCCCATCCGGACCCCTAGCCGGAGCATGC
CGCCCCTGGACCAGCCGAGCTGCAAGGCGCTGTACGACTTCGAGCCCGAGAACGACGGGGAGCTGGGCT
TCCATGAGGGCGACGTCATCACGCTGACCAACCAGATCGATGAGAACTGGTACGAGGGCATGCTGGACGG
CCAGTCGGGCTTCTTCCCGCTCAGCTACGTGGAGGTGCTTGTGCCCCTGCCGCAG
Protein Sequence **(Seq ID No. 30)***:*
>sp|Q99961|SH3G1_HUMAN Endophilin-A2 OS=Homo sapiens OX=9606 GN=SH3GL1 PE=1 SV=1

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SKIRGQVKNPGYPQSEGLLGECMIRHGKELGGESNFGDALLDAGESMKRLAEVKDSLDIEVKQNFIDPLQNLCEK
DLKEIQHHLKKLEGRRLDFDYKKKRQGKIPDEELRQALEKFEESKEVAETSMHNLLETDIEQVSQLSALVDAQLDY
HRQAVQILDELAEKLKRRMREASSRPKREYKPKPREPFDLGEPEQSNGGFPCTTAPKIAASSSFRSSDKPIRTPS
RSMPPLDQPSCKALYDFEPENDGELGFHEGDVITLTNQIDENWYEGMLDGQSGFFPLSYVEVLVPLPQ

FN3K Q9H479 Fructosamine-3-kinase

Nucleotide Sequence **(Seq ID No. 10)***:*
>P002359_Q106_Q106p1_FN3K_64122_Homo sapiens fructosamine 3 kinase_BC042680.1_AAH42680.1_Q9H479_0_0_930_0_927

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CAGGCCCGGCAGATGTTTGAGGGGGAGGTGGCCAGCCTGGAGGCCCTCCGGAGCACGGGCCTGGTGCG
GGTGCCGAGGCCCATGAAGGTCATCGACCTGCCGGGAGGTGGGGCCGCCTTTGTGATGGAGCATTTGAAG
ATGAAGAGCTTGAGCAGTCAAGCATCAAAACTTGGAGAGCAGATGGCAGATTTGCATCTTTACAACCAGAAG
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TGGACAAGTTCGGCTTCCACACGGTGACGTGCTGCGGCTTCATCCCGCAGGTGAATGAGTGGCAGGATGA

CTGGCCGACCTTTTTCGCCCGGCACCGGCTCCAGGCGCAGCTGGACCTCATTGAGAAGGACTATGCTGAC
CGAGAGGCACGAGAACTCTGGTCCCGGCTACAGGTGAAGATCCCGGATCTGTTTTGTGGCCTAGAGATTGT
CCCCGCGTTGCTCCACGGGGATCTCTGGTCGGGAAACGTGGCTGAGGACGACGTGGGGCCCATTATTTAC
GACCCGGCTTCCTTCTATGGCCATTCCGAGTTTGAACTGGCAATCGCCTTGATGTTTGGGGGGTTCCCCAG
ATCCTTCTTCACCGCCTACCACCGGAAGATCCCCAAGGCTCCGGGCTTCGACCAGCGGCTGCTGCTCTACC
AGCTGTTTAACTACCTGAACCACTGGAACCACTTCGGGCGGGAGTACAGGAGCCCTTCGTTGGGCACCATG
CGAAGGCTGCTCAAG

Protein Sequence **(Seq ID No. 31)**:
>sp|Q9H479|FN3K_HUMAN Fructosamine-3-kinase OS=Homo sapiens OX=9606 GN=FN3K PE=1 SV=1

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MKVIDLPGGGAAFVMEHLKMKSLSSQASKLGEQMADLHLYNQKLREKLKEEENTVGRRGEGAEPQYVDKFGFH
TVTCCGFIPQVNEWQDDWPTFFARHRLQAQLDLIEKDYADREARELWSRLQVKIPDLFCGLEIVPALLHGDLWS
GNVAEDDVGPIIYDPASFYGHSEFELAIALMFGGFPRSFFTAYHRKIPKAPGFDQRLLLYQLFNYLNHWNHFGRE
YRSPSLGTMRRLLK

PANK3 Q9H999 Pantothenate kinase 3

Nucleotide Sequence **(Seq ID No. 11)**:
>P002239_Q106_Q106p2_PANK3_79646_Homo sapiens pantothenate kinase
3_BC013705.1_AAH13705.1_Q9H999_0_0_1113_0_1110

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GGAAATATTTGACTTCTAACGTGGCATATGGATCCACCGGCATTCGGGATGTACACCTTGAACTGAAAGATT
TAACACTTTTTGGCCGAAGAGGGAACTTGCACTTTATCAGGTTTCCAACCCAGGACCTGCCTACTTTTATCCA
AATGGGAAGAGATAAAAACTTCTCAACATTGCAGACGGTGCTATGTGCTACAGGAGGTGGTGCTTACAAGTT
TGAAAAAGATTTTCGCACAATTGGAAACCTCCACCTGCACAAACTGGATGAACTTGACTGCCTTGTAAAGGG
CTTGCTGTATATAGACTCTGTCAGTTTCAATGGACAAGCCGAGTGCTATTATTTTGCTAATGCCTCAGAACCT
GAGCGATGCCAAAAGATGCCTTTTAACCTGGATGATCCCTATCCACTGCTTGTAGTGAACATTGGCTCAGGA
GTCAGTATTTTAGCAGTCCATTCCAAAGACAACTATAAACGAGTGACTGGGACAAGCCTTGGAGGGGGTAC
CTTTCTGGGTTTATGCAGTTTATTGACTGGCTGTGAAAGTTTTGAAGAGGCTCTTGAAATGGCATCCAAAGGT
GATAGCACACAAGCTGACAAGCTGGTCCGTGATATTTATGGAGGAGATTATGAAAGATTTGGTTTGCCAGGT
TGGGCTGTAGCATCTAGTTTTGGGAATATGATTTATAAGGAGAAGCGAGAATCTGTTAGTAAAGAAGATCTG
GCAAGAGCTACTTTAGTTACTATCACCAATAACATTGGTTCTGTGGCACGAATGTGTGCTGTTAATGAGAAAA
TAAACAGAGTTGTCTTTGTTGGAAACTTTTTACGTGTCAATACCCTCTCAATGAAACTTTTGGCATATGCACT
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ACTTCTTGGGCTGCCAAATTTCAGC

Protein Sequence **(Seq ID No. 32)**:
>sp|Q9H999|PANK3_HUMAN Pantothenate kinase 3 OS=Homo sapiens OX=9606 GN=PANK3 PE=1 SV=1

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RRGNLHFIRFPTQDLPTFIQMGRDKNFSTLQTVLCATGGGAYKFEKDFRTIGNLHLHKLDELDCLVKGLLYIDSVS
FNGQAECYYFANASEPERCQKMPFNLDDPYPLLVVNIGSGVSILAVHSKDNYKRVTGTSLGGGTFLGLCSLLTGC
ESFEEALEMASKGDSTQADKLVRDIYGGDYERFGLPGWAVASSFGNMIYKEKRESVSKEDLARATLVTITNNIGS
VARMCAVNEKINRVVFVGNFLRVNTLSMKLLAYALDYWSKGQLKALFLEHEGYFGAVGALLGLPNFS

HPCAL1 P37235 Hippocalcin-like protein 1

Nucleotide Sequence **(Seq ID No. 12)**:
>P003172_Q311_Q311_tube_HPCAL1_3241_0_NM_002149.2_0_P37235_0

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ACCACGAGCTGCAAGAGTGGTACAAGGGTTTCCTGAAGGACTGCCCCACCGGTCACCTGACCGTGGACGA
GTTCAAGAAGATCTACGCTAACTTCTTCCCCTACGGCGACGCTTCCAAGTTCGCTGAGCACGTGTTCCGTAC

CTTCGACACCAACGGCGACGGCACCATCGACTTCCGCGAGTTCATCATCGCTCTGTCCGTGACCTCCCGTG
GCAAGCTCGAGCAAAAGCTGAAGTGGGCTTTCTCGATGTACGACCTGGACGGCAACGGTTACATCTCCCGT
TCCGAGATGCTCGAGATCGTGCAGGCTATCTACAAGATGGTGTCCTCCGTGATGAAGATGCCCGAGGACGA
GTCCACCCCCGAGAAGCGTACCGACAAGATCTTCCGTCAGATGGACACCAACAACGACGGAAAGCTGTCCC
TGGAAGAGTTCATCCGTGGTGCTAAGTCCGACCCCTCCATCGTGCGTCTGCTGCAGTGCGACCCATCCTCC
GCTTCCCAGTTC

Protein Sequence **(Seq ID No. 33)***:*
>sp|P37235|HPCL1_HUMAN Hippocalcin-like protein 1 OS=Homo sapiens OX=9606 GN=HPCAL1 PE=1 SV=3

MGKQNSKLRPEVLQDLRENTEFTDHELQEWYKGFLKDCPTGHLTVDEFKKIYANFFPYGDASKFAEHVFRTFDT
NGDGTIDFREFIIALSVTSRGKLEQKLKWAFSMYDLDGNGYISRSEMLEIVQAIYKMVSSVMKMPEDESTPEKRTD
KIFRQMDTNNDGKLSLEEFIRGAKSDPSIVRLLQCDPSSASQF

THRA P10827 Thyroid hormone receptor alpha

Nucleotide Sequence **(Seq ID No. 13)***:*
>P000757_TRN_TRNp2_THRA_7067_Homo sapiens Homo sapiens thyroid hormone receptor alpha (erythroblastic leukemia viral (v-erb-a) onc_BC000261.1_AAH00261.1_P10827_0_0_1473_0_1470

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GAAAGCGAAAAAGAAAGAACGGCCAATGTTCCCTGAAAACCAGCATGTCAGGGTATATCCCTAGTTACCTG
GACAAAGACGAGCAGTGTGTCGTGTGTGGGGACAAGGCAACTGGTTATCACTACCGCTGTATCACTTGTGA
GGGCTGCAAGGGCTTCTTTCGCCGCACAATCCAGAAGAACCTCCATCCCACCTATTCCTGCAAATATGACA
GCTGCTGTGTCATTGACAAGATCACCCGCAATCAGTGCCAGCTGTGCCGCTTCAAGAAGTGCATCGCCGTG
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TGTCCCTGCGGGCGGCTGTCCGCTACGACCCTGAGAGCGACACCCTGACGCTGAGTGGGGAGATGGCTGT
CAAGCGGGAGCAGCTCAAGAATGGCGGCCTGGGCGTAGTCTCCGACGCCATCTTTGAACTGGGCAAGTCA
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ACAGCAGCTTCTCGGAATGCATGTTGTTCAGGGTCCGCAGGTCCGGCAGCTTGAGCAGCAGCTTGGTGAA
GCGGGAAGTCTCCAAGGGCCGGTTCTTCAGCACCAGAGCCCGAAGAGCCCGCAGCAGCGTCTCCTGGAG
CTGCTCCACCGAAGCGGAATTCTCCATGCCCGAGCGGTCTGTGGGGAAGACGACAGCAGTGAGGCGGACT
CCCCGAGCTCCTCTGAGGAGGAACCGGAGGTCTGCGAGGACCTGGCAGGCAATGCAGCCTCTCCC

Protein Sequence **(Seq ID No. 34)***:*
>sp|P10827|THA_HUMAN Thyroid hormone receptor alpha OS=Homo sapiens OX=9606 GN=THRA PE=1 SV=1

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KGFFRRTIQKNLHPTYSCKYDSCCVIDKITRNQCQLCRFKKCIAVGMAMDLVLDDSKRVAKRKLIEQNRERRRKE
EMIRSLQQRPEPTPEEWDLIHIATEAHRSTNAQGSHWKQRRKFLPDDIGQSPIVSMPDGDKVDLEAFSEFTKIITP
AITRVVDFAKKLPMFSELPCEDQIILLKGCCMEIMSLRAAVRYDPESDTLTLSGEMAVKREQLKNGGLGVVSDAIF
ELGKSLSAFNLDDTEVALLQAVLLMSTDRSGLLCVDKIEKSQEAYLLAFEHYVNHRKHNIPHFWPKLLMKEREVQ
SSILYKGAAAEGRPGGSLGVHPEGQQLLGMHVVQGPQVRQLEQQLGEAGSLQGPVLQHQSPKSPQQRLLELL
HRSGILHARAVCGEDDSSEADSPSSSEEEPEVCEDLAGNAASP

AIFM1 O95831 Apoptosis-inducing factor 1, mitochondrial

Nucleotide Sequence **(Seq ID No. 14)***:*

>P003305_Q311_Q311_tube_AIFM1_9131_Apoptosis-inducing factor, mitochondrion-associated, 1 [Homo sapiens]_NM_001130846.2_0_0_0_0_0_0_0

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CCTCGAGCCCAACGTCGAGCTGGCTAAGACCGGTGGCCTCGAGATCGACTCCGACTTCGGTGGTTTCCGT
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GCTGGGTCGTCGTCGTGTCGAGCACCACGACCACGCTGTGGTGTCCGGTCGTCTGGCTGGCGAGAACATG
ACCGGTGCTGCTAAGCCCTACTGGCACCAGTCCATGTTCTGGTCCGACCTGGGTCCCGACGTGGGTTACG
AGGCTATCGGCCTGGTGGACTCCTCCCTGCCCACCGTGGGAGTGTTCGCTAAGGCTACCGCTCAGGACAA
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GTGTCATCTTCTACCTGCGTGACAAGGTGGTCGTGGGTATCGTGCTGTGGAACATCTTCAACCGTATGCCTA
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CCACGAGGAC

Protein Sequence **(Seq ID No. 35)**:
>splO95831lAIFM1_HUMAN Apoptosis-inducing factor 1, mitochondrial OS=Homo sapiens OX=9606 GN=AIFM1 PE=1 SV=1

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RSIRARDPGARVLIVSEDPELPYMRPPLSKELWFSDDPNVTKTLRFKQWNGKERSIYFQPPSFYVSAQDLPHIEN
GGVAVLTGKKVVQLDVRDNMVKLNDGSQITYEKCLIATGGTPRSLSAIDRAGAEVKSRTTLFRKIGDFRSLEKISR
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SSGKLLIKLKDGRKVETDHIVAAVGLEPNVELAKTGGLEIDSDFGGFRVNAELQARSNIWVAGDAACFYDIKLGRR
RVEHHDHAVVSGRLAGENMTGAAKPYWHQSMFWSDLGPDVGYEAIGLVDSSLPTVGVFAKATAQDNPKSATE
QSGTGIRSESETESEASEITIPPSTPAVPQAPVQGEDYGKGVIFYLRDKVVVGIVLWNIFNRMPIARKIIKDGEQHE
DLNEVAKLFNIHED

ODC1 P11926 Ornithine decarboxylase

Nucleotide Sequence **(Seq ID No. 15)**:
>P000568_SIG_SIG1-3_ODC1_4953_Homo sapiens ornithine decarboxylase 1_BC025296.1_AAH25296.1_P11926_62117_0_1386_0_1383

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CGTCAGACTCTGGAGTGAGAATCATAGCTGAGCCCGGCAGATACTATGTTGCATCAGCTTTCACGCTTGCA
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Protein Sequence **(Seq ID No. 36):**
>sp|P11926|DCOR_HUMAN Ornithine decarboxylase OS=Homo sapiens OX=9606 GN=ODC1 PE=1 SV=2

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VLRIATDDSKAVCRLSVKFGATLRTSRLLLERAKELNIDVVGVSFHVGSGCTDPETFVQAISDARCVFDMGAEVG
FSMYLLDIGGGFPGSEDVKLKFEEITGVINPALDKYFPSDSGVRIIAEPGRYYVASAFTLAVNIIAKKIVLKEQTGSD
DEDESSEQTFMYYVNDGVYGSFNCILYDHAHVKPLLQKRPKPDEKYYSSSIWGPTCDGLDRIVERCDLPEMHVG
DWMLFENMGAYTVAAASTFNGFQRPTIYYVMSGPAWQLMQQFQNPDFPPEVEEQDASTLPVSCAWESGMKR
HRAACASASINV

RPS6KA4 O75676 Ribosomal protein S6 kinase alpha-4

Nucleotide Sequence **(Seq ID No. 16):**
>P001321_Q305_Q305p4_RPS6KA4_8986_Homo sapiens RPS6KA4 ribosomal protein S6 kinase, 90kDa, polypeptide 4_BC047896_AAH47896_O75676_0_0_1575_0_1572

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CGGGAGGGCTTCTTCCTGAAGAGCGTGGAGAACGCACCCCTGGCCAAGCGGCGGAAGCAGAAGCTGCGG
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Protein Sequence **(Seq ID No. 37)***:*
>sp|O75676|KS6A4_HUMAN Ribosomal protein S6 kinase alpha-4 OS=Homo sapiens OX=9606 GN=RPS6KA4 PE=1 SV=1

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TQREVAALRLCQSHPNVVNLHEVHHDQLHTYLVLELLRGGELLEHIRKKRHFSESEASQILRSLVSAVSFMHEEA
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YMMLSGQVPFQGASGQGGQSQAAEIMCKIREGRFSLDGEAWQGVSEEAKELVRGLLTVDPAKRLKLEGLRGSS
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EEF1D P29692 Elongation factor 1-delta

Nucleotide Sequence **(Seq ID No. 17)***:*
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Protein Sequence **(Seq ID No. 38):**
>sp|P29692|EF1D_HUMAN Elongation factor 1-delta OS=Homo sapiens OX=9606 GN=EEF1D PE=1 SV=5

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AEDDEDDDIDLFGSDNEEEDKEAAQLREERLRQYAEKKAKKPALVAKSSILLDVKPWDDETDMAQLEACVRSIQL
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KLF10 Q13118 Krueppel-like factor 10

Nucleotide Sequence **(Seq ID No. 18)***:*
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Protein Sequence **(Seq ID No. 39):**
>sp|Q13118|KLF10_HUMAN Krueppel-like factor 10 OS=Homo sapiens OX=9606 GN=KLF10 PE=1 SV=1

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AQATSVIRHTADAQLCNHQTCPMKAASILNYQNNSFRRRTHLNVEAARKNIPCAAVSPNRSKCERNTVADVDEK
ASAALYDFSVPSSETVICRSQPAPVSPQQKSVLVSPPAVSAGGVPPMPVICQMVPLPANNPVVTTVVPSTPPSQ
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EPHA2 P29317 Ephrin type-A receptor 2

Nucleotide Sequence **(Seq ID No. 19)***:*
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Protein Sequence **(Seq ID No. 40):**
>sp|P29317|EPHA2_HUMAN Ephrin type-A receptor 2 OS=Homo sapiens OX=9606 GN=EPHA2 PE=1 SV=2

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PRKAR1A P10644 cAMP-dependent protein kinase type I-alpha regulatory subunit

Nucleotide Sequence **(Seq ID No. 20)***:*
>P000113_CAN_CAN1-1_PRKAR1A_5573_Homo sapiens protein kinase cAMP-dependent regulatory type I alpha (tissue specific e_BC036285.1_AAH36285.1_P10644_0_0_1146_0_1143

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Protein Sequence **(Seq ID No. 41):**
>sp|P10644|KAP0_HUMAN cAMP-dependent protein kinase type I-alpha regulatory subunit OS=Homo sapiens OX=9606 GN=PRKAR1A PE=1 SV=1

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SLSV

EAPP Q56P03 E2F-associated phosphoprotein

Nucleotide Sequence **(Seq ID No. 21)***:*
>P001616_Q106_Q106p2_EAPP_55837_Homo sapiens chromosome 14 open reading frame 11_BC001245.1_AAH01245.1_xx_0_0_858_0_855

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Protein Sequence **(Seq ID No. 42):**
>sp|Q56P03|EAPP_HUMAN E2F-associated phosphoprotein OS=Homo sapiens OX=9606 GN=EAPP PE=1 SV=4

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TMEDKLSSLGTGSSSGNGKVATAPTRYYDDIYFDSDSEDEDRAVQVTKKKKKKQHKIPTNDELLYDPEKDNRDQ
AWVDAQRRGYHGLGPQRSRQQQPVPNSDAVLNCPACMTTLCLDCQRHESYKTQYRAMFVMNCSINKEEVLRY
KASENRKKRRVHKKMRSNREDAAEKAETDVEEIYHPVMCTECSTEVAVYDKDEVFHFFNVLASHS

Claims

1. A method for predicting a response to adalimumab from a sample extracted from a rheumatoid arthritis patient prior to treating the patient with adalimumab, said response being classified as a good response corresponding to anti-drug antibody negative or a poor response corresponding to anti-drug antibody positive, comprising the steps of:

   (i) testing the sample for the presence of autoantibody biomarkers; and

   (ii) determining whether the patient will develop a good response or a bad response to treatment with adalimumab, based on the detection of said autoantibody biomarkers;

   characterised in that said autoantibody biomarkers comprise autoantibodies to antigens SSB, TROVE2 and ZHX2, wherein ZHX2 is associated with the good response, and SSB and TROVE2 are associated with the poor response.

2. The method according to claim 1 wherein the autoantibody biomarkers further comprise autoantibodies to one or more antigens from the group comprising of PPARD, SPANXN2, HNRNPA2B, TRIB2, CEP55, SH3GL1, FN3K, PANK3, HPCAL1, THRA, AIFM1, ODC1, RPS6KA4, EEF1D, KLF10, EPHA2, PRKAR1A and EAPP.

3. The method according to claim 1 or 2 wherein the antigens are biotinylated proteins.

4. The method according to claim 3 wherein each biotinylated protein is formed from a Biotin Carboxyl Carrier Protein folding marker which is fused in-frame with a protein.

5. The method according to claim 3 or 4 wherein the biotinylated proteins are bound to a streptavidin-coated substrate.

6. The method according to claim 5 wherein the substrate comprises a hydrogel-forming polymer base layer.

7. The method according to any preceding claim wherein the antigens are exposed to a sample extracted from a person, such that autoantibody biomarkers from the sample may bind to the antigens.

8. The method according to claim 7 wherein the antigens are subsequently exposed to a fluorescently-tagged secondary antibody to allow the amount of any autoantibodies from the sample bound to the antigens to be determined.

9. The method according to claim 8 wherein the patient's response to treatment with adalimumab corresponds to the relative or absolute amount of autoantibodies from the sample specifically binding to the antigens.

10. The method according to any preceding claim wherein the sample comprises any or any combination of exosomes, blood, serum, plasma, urine, saliva, amniotic fluid, cerebrospinal fluid, breast milk, semen or bile.

11. The method according to any preceding claim wherein the steps are performed *in vitro*.

12. The method according to any preceding claim wherein the method comprises detecting upregulation/downregulation of one or more biomarkers.

13. A method for manufacturing a kit for predicting a response to adalimumab from a sample extracted from a rheumatoid arthritis patient prior to treating the patient with adalimumab, comprising the steps of:

for each antigen in a panel, cloning a biotin carboxyl carrier protein folding marker in-frame with a gene encoding the antigen and expressing the resulting biotinylated antigen;

binding the biotinylated antigens to addressable locations on one or more streptavidin-coated substrates, thereby forming an antigen array;

such that the amount of autoantibodies from the sample binding to the antigens on the panel can be determined by exposing the substrate to the sample and measuring the response;

characterised in that the antigens comprise SSB, TROVE2 and ZHX2.

14. The method according to claim 13 wherein the antigens further comprise one or more of PPARD, SPANXN2, HNRNPA2B, TRIB2, CEP55, SH3GL1, FN3K, PANK3, HPCAL1, THRA, AIFM1, ODC1, RPS6KA4, EEF1D, KLF10, EPHA2, PRKAR1A and EAPP.

15. A composition comprising a panel of antigens for predicting an immunogenic and/or therapeutic response to adalimumab in a rheumatoid arthritis patient who has not previously been treated with adalimumab, characterised in that the antigens comprise SSB, TROVE2 and ZHX2.

16. A composition according to claim 15 wherein the antigens further comprise one or more of PPARD, SPANXN2, HNRNPA2B, TRIB2, CEP55, SH3GL1, FN3K, PANK3, HPCAL1, THRA, AIFM1, ODC1, RPS6KA4, EEF1D, KLF10, EPHA2, PRKAR1A and EAPP.

17. A composition according to claim 15 or 16 wherein the antigens are biotinylated proteins.

18. A composition according to any of claims 15-17 wherein the amount of one or more autoantibody biomarkers binding *in vitro* to the antigens in a sample from a patient can be measured to predict the response.

19. A composition comprising a panel of autoantibody biomarkers for predicting an immunogenic and/or therapeutic response to adalimumab in a rheumatoid arthritis

patient who has not previously been treated with adalimumab, wherein the level of the autoantibody biomarkers are measured in a sample collected from the patient;

characterised in that the autoantibody biomarkers are specific to antigens comprising SSB, TROVE2 and ZHX2.

5

Figure 1

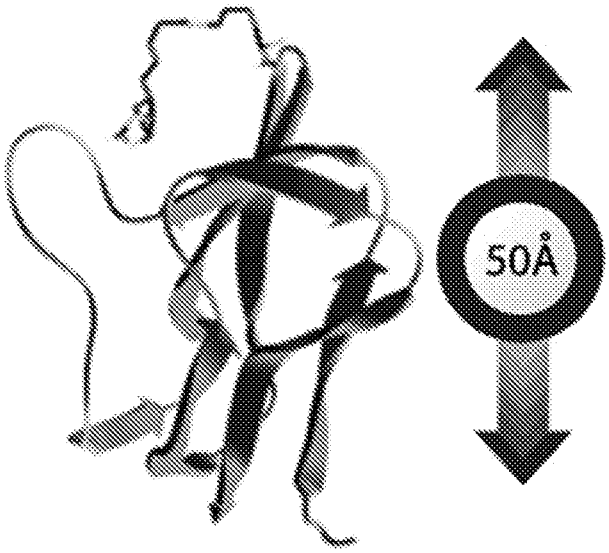


Figure 2

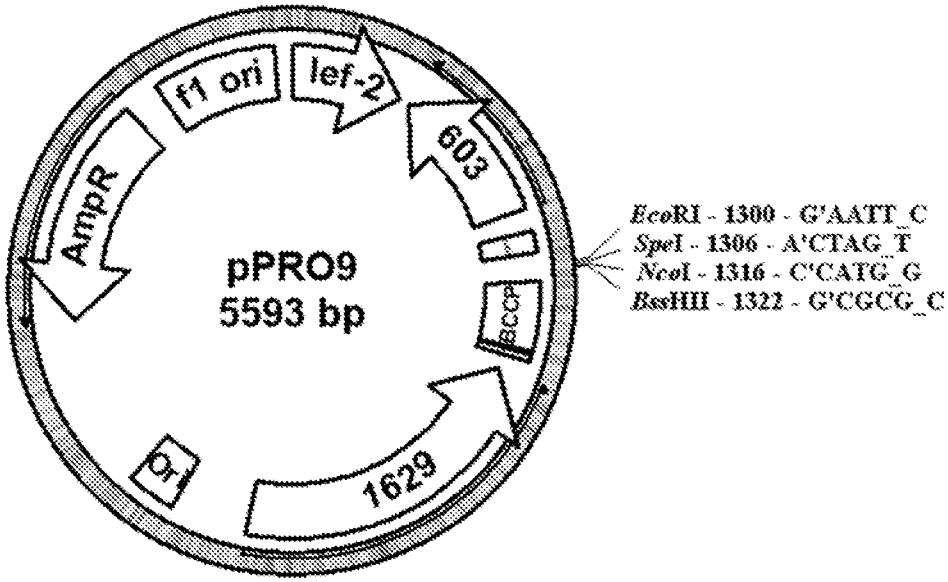


Figure 3

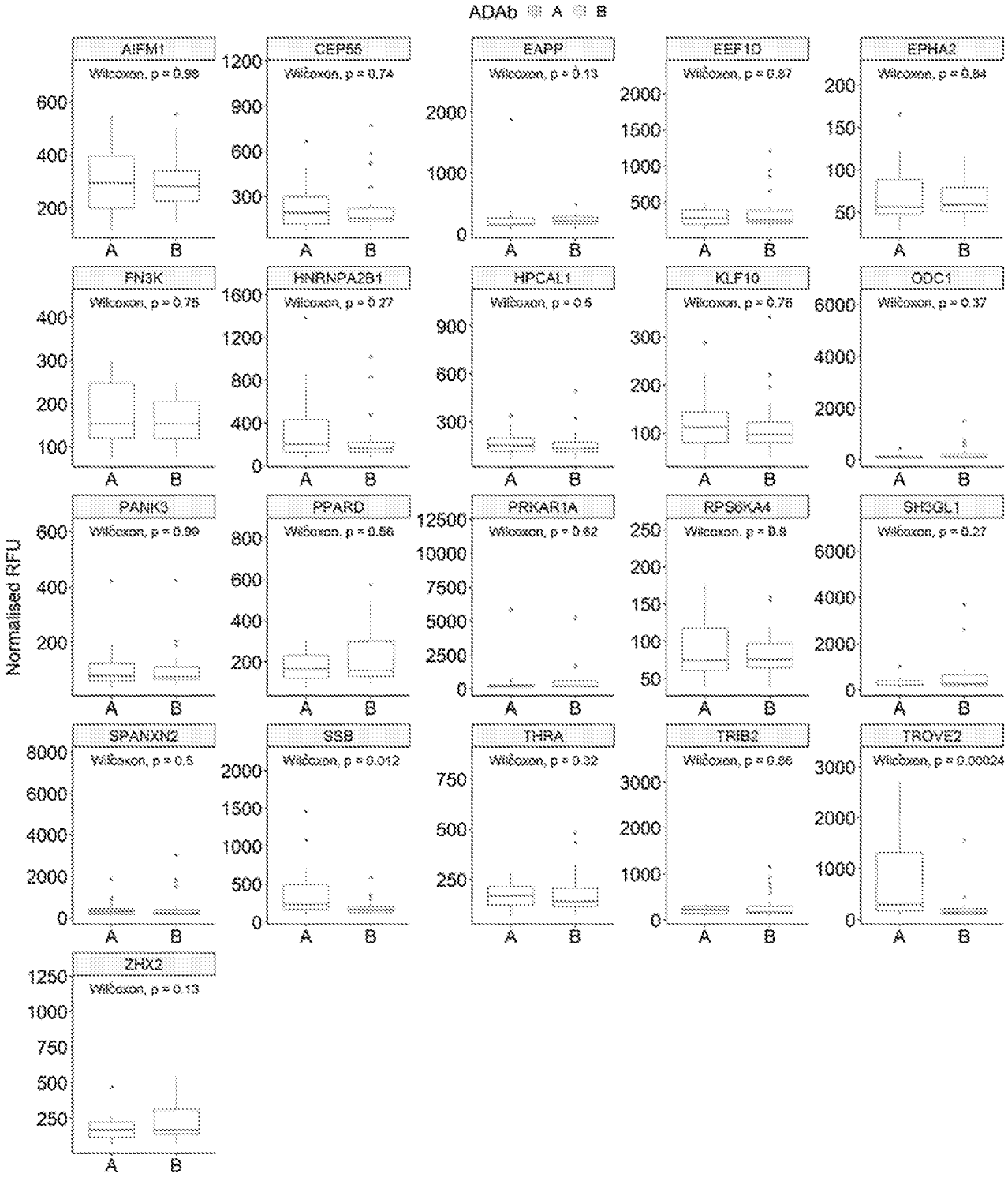

ADAb A B
Normalised RFU
AIFM1
Wilcoxon, p = 0.98
CEP55
Wilcoxon, p = 0.74
EAPP
Wilcoxon, p = 0.13
EEF1D
Wilcoxon, p = 0.87
EPHA2
Wilcoxon, p = 0.84
FN3K
Wilcoxon, p = 0.75
HNRNPA2B1
Wilcoxon, p = 0.27
HPCAL1
Wilcoxon, p = 0.5
KLF10
Wilcoxon, p = 0.76
ODC1
Wilcoxon, p = 0.37
PANK3
Wilcoxon, p = 0.99
PPARD
Wilcoxon, p = 0.56
PRKAR1A
Wilcoxon, p = 0.62
RPS6KA4
Wilcoxon, p = 0.9
SH3GL1
Wilcoxon, p = 0.27
SPANXN2
Wilcoxon, p = 0.5
SSB
Wilcoxon, p = 0.012
THRA
Wilcoxon, p = 0.32
TRIB2
Wilcoxon, p = 0.86
TROVE2
Wilcoxon, p = 0.00024
ZHX2
Wilcoxon, p = 0.13
A
B

Figure 4

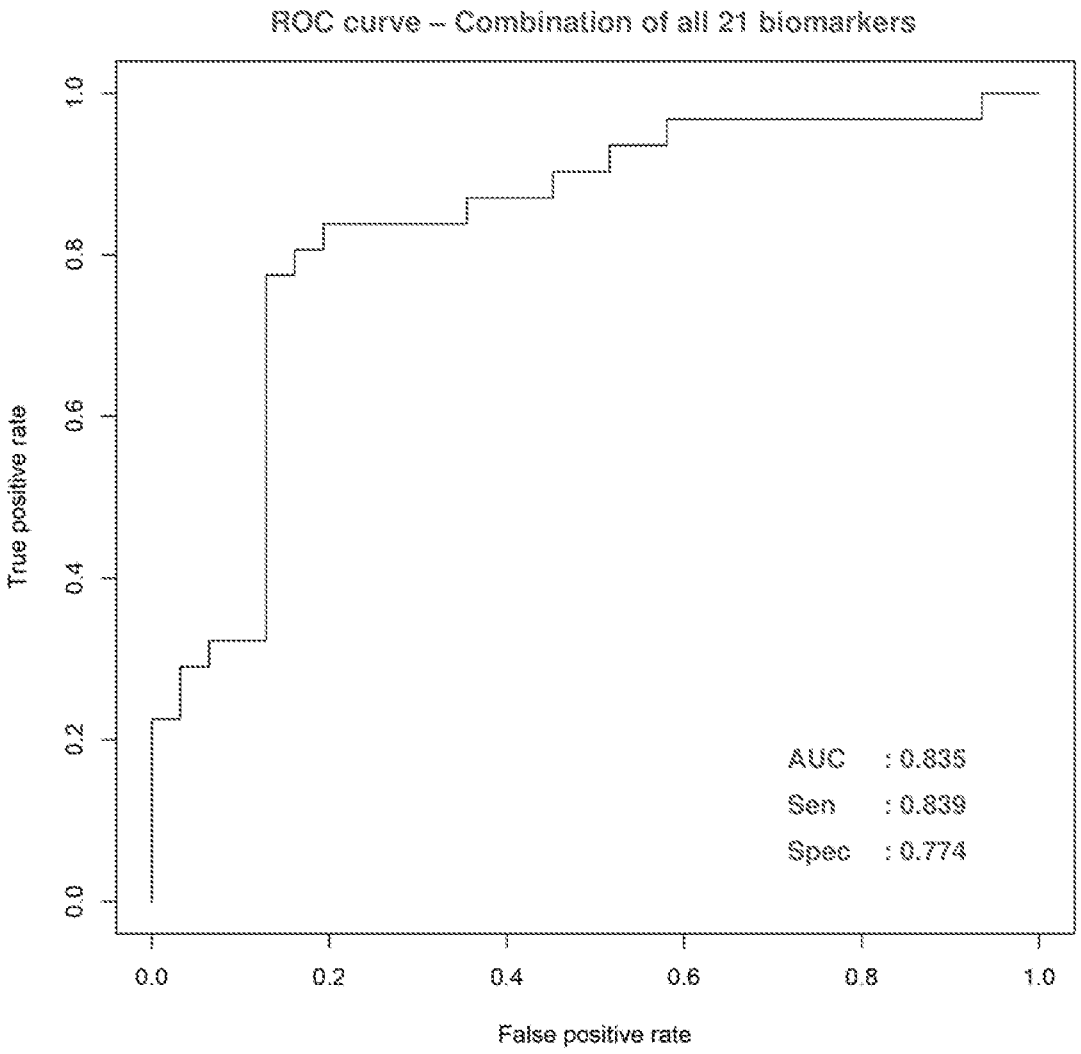

ROC curve – Combination of all 21 biomarkers
True positive rate
False positive rate
0.0
0.2
0.4
0.6
0.8
1.0
AUC : 0.835
Sen : 0.839
Spec : 0.774

Figure 5

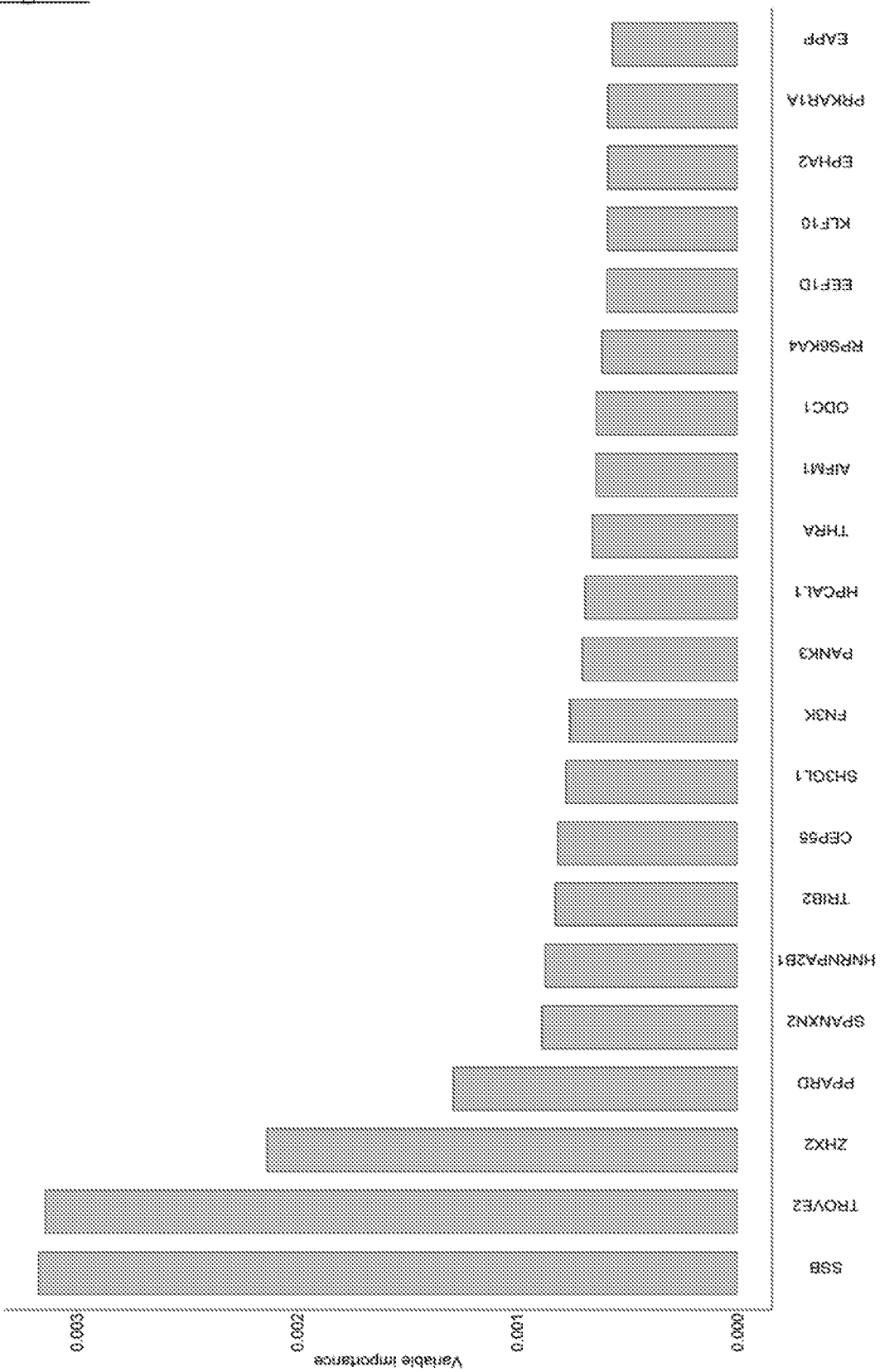
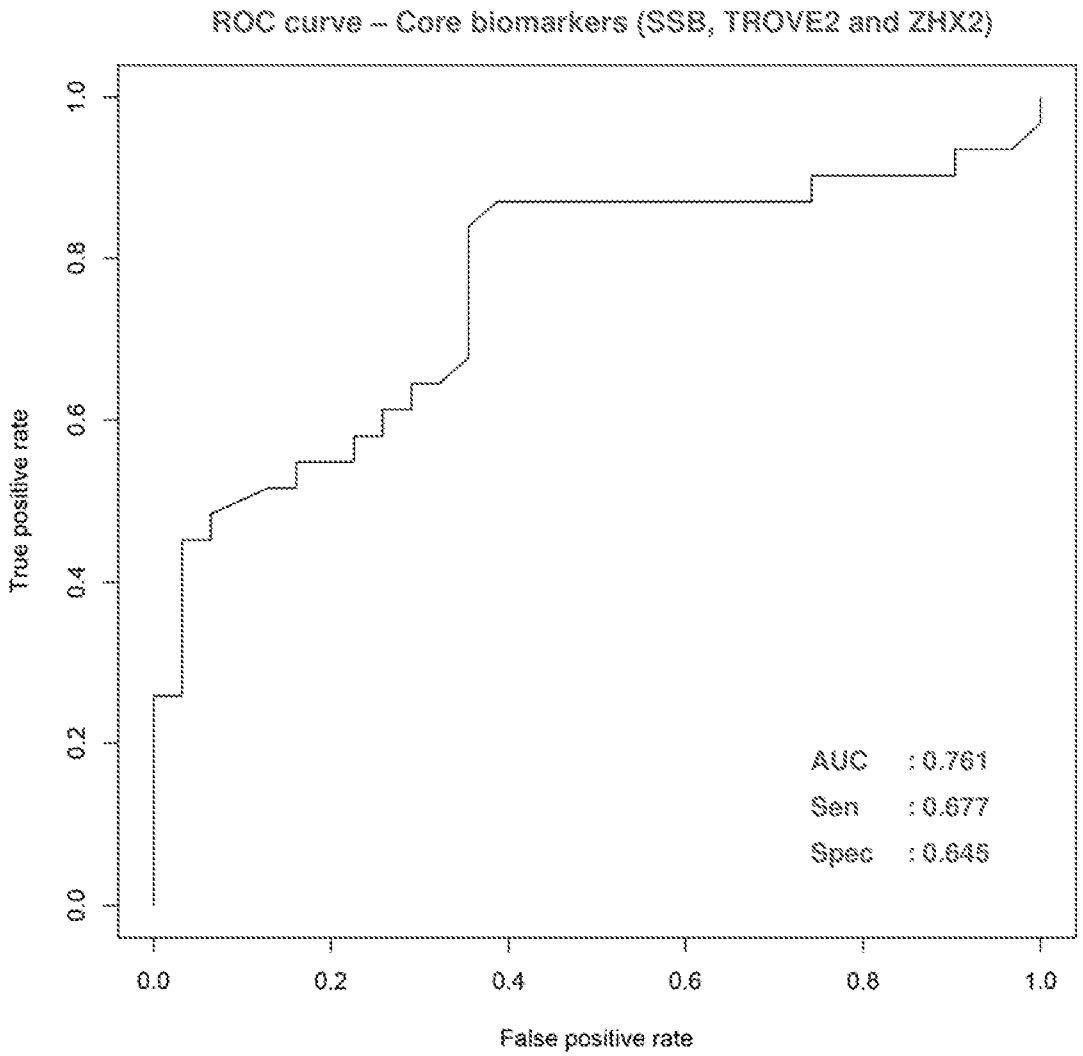

Variable importance
0.000
0.001
0.002
0.003
S58
TROVE2
ZHX2
PPARD
SPANXN2
HNRNPA2B1
TRIB2
CEP55
SH3GL1
FN3K
PANK3
HPCAL1
THRA
AIFM1
ODC1
RPS6KA4
EEF1D
KLF10
EPHA2
PRKAR1A
EAPP

Figure 6


ROC curve – Core biomarkers (SSB, TROVE2 and ZHX2)
True positive rate
False positive rate
0.0
0.2
0.4
0.6
0.8
1.0
AUC : 0.761
Sen : 0.677
Spec : 0.645

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SG2021/050690

A. CLASSIFICATION OF SUBJECT MATTER

G01N 33/68 (2006.01) G01N 33/564 (2006.01)

According to International Patent Classification (IPC)

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

G01N C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

FAMPAT/EMBASE/BIOSIS/MEDLINE: SSB, TROVE2, ZHX2, adalimumab, rheumatoid arthritis, autoantibody, and related terms

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	Immunome™. 4 July 2018 [Retrieved on 2022-01-19 from https://hoc.bme.uh.edu/services/autoantibody-screening-autoantigen-arrays/immunome/] Link to Excel spreadsheet containing all >1600 targets of the IMMUNOME™ v4 Discovery Array	15-18 13-14
X A	ORTEA I. ET AL., Independent Candidate Serum Protein Biomarkers of Response to Adalimumab and to Infliximab in Rheumatoid Arthritis: An Exploratory Study. *PLoS One.*, 6 April 2016, Vol. 11, No. 4, pages e0153140 (1-13) [Retrieved on 2022-01-19] <DOI: 10.1371/JOURNAL.PONE.0153140> Whole document	19 1-12

☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

*Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"D" document cited by the applicant in the international application

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19/01/2022 *(day/month/year)*	*31/01/2022* *(day/month/year)*

Name and mailing address of the ISA/SG	Authorized officer
Intellectual Property Office of Singapore 1 Paya Lebar Link, #11-03 PLQ 1, Paya Lebar Quarter Singapore 408533	Wang Yanyao (Ms)
Email: pct@ipos.gov.sg	IPOS Customer Service Tel. No.: (+65) 6339 8616

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X A	MATSUDAIRA R. ET AL., Anti-Ro/SSA antibodies are an independent factor associated with an insufficient response to tumor necrosis factor inhibitors in patients with rheumatoid arthritis. *J Rheumatol.*, 1 October 2011, Vol. 38, No. 11, pages 2346-2354 [Retrieved on 2022-01-19] <DOI: 10.3899/JRHEUM.101295.> Whole document	19 1-12
Y	WO 03/064656 A1 (SENSE PROTEOMIC LIMITED) 7 August 2003 Page 3 lines 5-11 and Examples 1-2	13-14
P,X	CHEN P. K. ET AL., Anti-TROVE2 Antibody Determined by Immune-Related Array May Serve as a Predictive Marker for Adalimumab Immunogenicity and Effectiveness in RA. *J Immunol Res.*, 8 March 2021, Vol. 2021, pages 6656121 (1-13) [Retrieved on 2022-01-19] <DOI: 10.1155/2021/6656121.> Whole document	1-12 and 15-19
P,A	MORI A. ET AL., Presence of anti-nuclear antibodies is a risk factor for the appearance of anti-drug antibodies during infliximab or adalimumab therapy in patients with rheumatoid arthritis. *PLoS One.*, 14 December 2020, Vol. 5, No. 12, pages e0243729 (1-16) [Retrieved on 2022-01-19] <DOI: 10.1371/JOURNAL.PONE.0243729> Whole document	-

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SG2021/050690

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

   a. ☐ forming part of the international application as filed:

      ☐ in the form of an Annex C/ST.25 text file.

      ☐ on paper or in the form of an image file.

   b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. ☐ furnished subsequent to the international filing date for the purposes of international search only:

      ☐ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

2. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

   Although a sequence listing has been filed or furnished, it was not used for the purposes of this search.

   Since only one version or copy of a sequence listing has been filed or furnished, the statements under item 2 are not required.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/SG2021/050690

Note: This Annex lists known patent family members relating to the patent documents cited in this International Search Report. This Authority is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 03/064656 A1	07/08/2003	AU 2003238441 B2	30/10/2008
		WO 03064656 A1	07/08/2003
		ES 2268376 T3	16/03/2007
		EP 1470229 A1	27/10/2004
		DE 60305643 T2	03/05/2007
		CA 2474457 A1	07/08/2003
		JP 2005516074 A	02/06/2005
		DK 1470229 T3	02/10/2006
		AT 328092 T	15/06/2006
		US 2005/0221308 A1	06/10/2005