Blood-based immune-endocrine biomarkers of treatment response in depression

Running title: Blood-based biomarkers of treatment response in depression

Man K. Chan (PhD)[1], Jason D. Cooper (PhD)[1], Mariska Bot (PhD)[2], Tom K. Birkenhager (MD, PhD)[3], Veerle Bergink (MD, PhD)[3], Hemmo A. Drexhage (MD, PhD)[3], Johann Steiner (MD, PhD)[4], Matthias Rothermundt (MD, PhD)[5], Brenda WJH Penninx (PhD)[2], Sabine Bahn (MD, PhD)[1*]

[1]Department of Chemical Engineering and Biotechnology, University of Cambridge, Cambridge, United Kingdom
[2]Department of Psychiatry, EMGO Institute for Health and Care Research and Neuroscience Campus Amsterdam, VU University Medical Centre, Amsterdam, The Netherlands
[3]Department of Psychiatry and Immunology, Erasmus Medical Center, Rotterdam, The Netherlands
[4]Department of Psychiatry, University of Magdeburg, Germany
[5]Department of Psychiatry, University of Muenster, Germany and Evangelisches Klinikum Niederrhein, Oberhausen, Germany

***Correspondence to:**
Professor Sabine Bahn, Department of Chemical Engineering and Biotechnology, University of Cambridge, Tennis Court Road, Cambridge, CB2 1QT, United Kingdom. Tel: +44 1223 334 151, Fax: +44 1223 334 162, Email: **sb209@cam.ac.uk**

Revised manuscript word count
Abstract: 247
Main text: 4395
Figures/Tables: 1/2

Abstract

Antidepressant treatment for major depressive disorder remains suboptimal with response rates of just over 50%. Although treatment guidelines, algorithms and clinical keys are available to assist the clinician, the process of finding an effective pharmacotherapy to maximise benefit for the individual patient is largely by "trial and error" and remains challenging. This highlights a clear need to identify biomarkers of treatment response to help guide personalised treatment strategies. We have carried out the largest multiplex immunoassay based longitudinal study to date, examining up to 258 serum markers involved in immune, endocrine and metabolic processes as potential biomarkers associated with treatment response in 332 depression patients recruited from four independent clinical centres. We demonstrated for the first time that circulating Apolipoprotein A-IV, Endoglin, Intercellular Adhesion Molecule 1, Tissue Inhibitor of Metalloproteinases 1, Plasminogen Activator Inhibitor 1, Thrombopoietin, Complement C3, Hepatocyte Growth Factor and Insulin-like Growth Factor-Binding Protein 2 were associated with response to different antidepressants. In addition, we showed that specific sets of immune-endocrine proteins were associated with response to Venlafaxine (serotonin–norepinephrine reuptake inhibitor), Imipramine (tricyclic antidepressant) and other antidepressant drugs. However, we were not able to reproduce the literature findings on BDNF and TNF-α, two of the most commonly reported candidate treatment response markers. Despite the need for extensive validation studies, our preliminary findings suggest that a pre-treatment immune-endocrine profile may help to determine a patient's likelihood to respond to specific antidepressant and/or alternative treatments such as anti-inflammatory drugs, providing hope for future personalised treatment approaches.

Keywords: Depression; Antidepressant Treatment Response; SNRI; TCA; Blood-based; Biomarker

Introduction

Antidepressant drugs are currently the mainstay of treatment for major depressive disorder (MDD). However, their effectiveness is suboptimal and highly variable due to disease heterogeneity and individual differences in drug metabolism, pharmacokinetics and toxicity (Miller and O'Callaghan, 2013). Although treatment guidelines (Maudsley (Taylor et al., 2015), NICE (NICE, 2010)), algorithms (Texas Medication Algorithm) (Suehs BT AT et al., 2008)) and clinical keys are available to assist the clinician to optimise outcome and reduce side-effects of treatment, the process of finding an effective pharmacotherapy to maximise benefit for the individual patient is largely by "trial and error" and remains challenging. Typically, it takes at least four weeks for an initial response to be observed and six to 12 weeks or more to attain remission with an initial antidepressant drug prescribed at an adequate dose (Rush et al., 2009). While response rates are on average 53.8% (37.3% for placebo response) (Papakostas and Fava, 2009), patients need to remain on an initially prescribed medication for many weeks to determine whether it will be effective. The non-responders are then prescribed another drug of the same or a different class, medication doses are adjusted and/or combinations are tested. This process may take many months until recovery is achieved (Keitner et al., 1992) and, many patients experience difficulty with side effects including weight gain, anxiety, decrease in libido and gastrointestinal symptoms. Crucially, the consequence of a lengthy treatment process is lack of medication compliance, which can result in poor treatment response. Large studies have shown that medication compliance drops significantly with duration of treatment (Olfson et al., 2006). Lack of compliance and failure to respond to antidepressants contribute heavily towards reduction of quality of life and productivity. Healthcare costs are also increased along with the risk of relapse and suicide (Miller and O'Callaghan, 2013).

As a result, the need to develop reliable treatment response predictors to guide personalised treatment strategies is becoming a pressing clinical need. Decades of research effort have now laid the foundation towards achieving this goal. Studies have consistently demonstrated molecular changes in both the central nervous system and the periphery in MDD patients (Chan et al., 2014; Kaestner et al., 2005), including alterations in the endocrine system involving the hypothalamic-pituitary-adrenal axis (HPA), carbohydrate/lipid metabolism and most prominently, the immune/inflammatory system. For instance, a

chronic low grade inflammatory response and activation of cell-mediated immunity is frequently observed in depression (Berk et al., 2013). Exogenous cytokine and endotoxin infusions have been found to induce depressive-like symptoms in some individuals (Udina et al., 2012). Antidepressant drugs have been shown to decrease production of pro-inflammatory cytokines and increase release of anti-inflammatory cytokines (Maes et al., 1999). Remission is often accompanied by a normalisation of inflammatory markers and non-response, at least in some cases, is associated with persistently elevated levels of such biomarkers (Hannestad et al., 2011). Anti-inflammatory drugs have also been found to ameliorate depressive symptoms in MDD patients, but these drugs may only be effective in specific subgroups of patients (Hashimoto, 2015).

The important question, which arises from these findings, is that it may be possible to sub-stratify patients based on their immune-endocrine profile. This differential profile could reflect the individual differences in efficacy and responses to antidepressant and/or anti-inflammatory drugs. Recently, a number of candidate treatment response predictors have been proposed including Brain-Derived Neurotrophic Factor (BDNF), Tumour Necrosis Factor Alpha (TNF-α), Interleukin-6 (IL-6), S100 calcium-binding protein B (S100-B) (Abou-Saleh et al., 1998; Papakostas, 2012), C-Reactive Protein (CRP) (Uher et al., 2014), Macrophage Migration Inhibitory Factor (MIF), Interleukin-1-β (IL-1β) (Cattaneo et al., 2016) and circulating leukocyte subpopulations (Grosse et al., 2016). Functional and structural brain imaging predictors have also been reported (Phillips et al., 2015). Studies examining pharmacological (drug-metabolizing enzymes) and genomic predictors have also shown promise (Leuchter et al., 2009). Nevertheless, to date, the most reliable predictors identified have been the symptomatic and physiologic features of patients that emerge early in the course of treatment, which unfortunately still lack sensitivity and specificity.

With this in mind, we carried out the largest multiplex immunoassay based study, to date, to identify candidate blood-based biomarkers of treatment response in serum from 332 MDD patients recruited from four independent clinical centres.

Materials and Methods

Clinical cohorts

MDD patients were recruited consecutively from four independent clinical centres. Cohorts 1 (n=30) and 2 (n=26) were from the Department of Psychiatry of the Erasmus Medical Center (MC), the Netherlands. Cohort 3 (n=38) was from the Department of Psychiatry, University of Magdeburg, Germany. Cohort 4 (n=21) was from the Department of Psychiatry, University of Muenster, Germany. Cohort 5 (n=217) consisted of a subset of the multi-site Netherlands Study of Depression and Anxiety (NESDA) cohort. Informed written consent was given by all participants. Study protocols, sample collection and analysis methods were approved by the respective institutional ethical committees and review boards and were in compliance with the Standards for Reporting of Diagnostic Accuracy (STARD) (Bossuyt et al., 2003). Patients from all cohorts were fasting at the time of blood collection. For cohorts 1-4, diagnosis was carried out using the Diagnostic and Statistical Manual of Mental Disorders, Text Revision (DSM-IV-TR)(API, 2000). Depression symptom severity was determined using the Hamilton Rating Scale for Depression, 17-item-version (HAMD) **(Table 1).**

The Erasmus MC patients were from a double-blind randomised clinical trial aimed to compare the efficacy of a plasma level-targeted dose of imipramine (tricyclic antidepressant (TCA)) and high-dose venlafaxine (serotonin-norepinephrine reuptake inhibitor (SNRI)) in severely depressed inpatients. For the present study, a subset of 56 patients from the trial was included based on availability of baseline serum samples. All patients were antidepressant medication free for at least one week prior to baseline assessment. Following baseline assessment, 30 patients were initiated on treatment with Venlafaxine (doses increased gradually to 300–375 mg/day, cohort 1) and 26 patients were initiated on treatment with Imipramine (doses adjusted to a blood level of 200–300 ng/ml, cohort 2) for seven weeks. Note that patients from the venlafaxine and imipramine arms are referred as cohorts 1 and 2, respectively, throughout the text to facilitate description of results and discussion.

Clinical assessments involved determination of psychiatric history, assessment of adequacy of treatment(s) in the current episode using the Antidepressant Treatment History Form, medical history and physical examination including vital signs and routine laboratory assessments. Exclusion criteria included

163 acute indication for electroconvulsive therapy (ECT), mental retardation, alcohol or substance dependence
164 within three months of enrolment, any serious chronic somatic illnesses or medications affecting mood and
165 contraindications for study medication. Notably, the percentage of patients from cohort 1 and 2 that took
166 anxiolytics (mostly lorazepam before the night, all of which stayed under the predefined maximum dosage
167 of lorazepam 3 mg) was 10%. The design of the main double-blind randomized clinical trial was previously
168 described in detail (Vermeiden et al., 2013).

169 The 38 patients from cohort 3 were either drug-naïve (n=27) or medication free for at least six
170 weeks (n=11) prior to baseline assessment. All 21 patients from cohort 4 were medication free for at least
171 one week prior to baseline interview. Following baseline assessment, patients from both cohorts 3 and 4
172 were initiated on mixed antidepressant treatment (i.e. different antidepressant drugs administered either
173 as monotherapy or combination therapy) for six and 4-26 weeks, respectively **(Table 1)**. The choice of
174 antidepressant medication regimen was based on psychiatrist's clinical experience. Information on
175 antidepressant medication use prior to hospitalisation was confirmed by direct contact with the treating
176 family physicians and relatives. Exclusion criteria included pregnant women, infections, immune and
177 autoimmune diseases, cancer or systemic diseases, cardiovascular disorders, diabetes, antibiotic and
178 immune -suppressant/-modulatory treatment, substance abuse, alcohol or drug addiction, renal
179 insufficiency, other neurologic or neuropsychiatric disorders and severe trauma. Exclusions were based on
180 self-report, physician's report or by physical examination.

181 Cohort 5 was a subset of the NESDA cohort, an ongoing multi-site naturalistic longitudinal cohort
182 study. This is a 2981 participant cohort (18–65 yrs), including 2329 individuals with lifetime or current
183 anxiety and/or depressive disorders and 652 healthy controls. Participants were recruited from the general
184 population, primary and specialised mental healthcare centres between 2004 and 2007. Exclusion criteria
185 at baseline included lack of fluency in Dutch or another primary clinical psychiatric disorder (e.g. bipolar,
186 psychotic, obsessive compulsive or severe addiction disorders). Details of the rationale, objectives and
187 methods of this study are reported elsewhere (Penninx et al., 2008). Diagnoses of MDD were based on the
188 Composite International Diagnostic Interview (CIDI), Lifetime Version 2.1 (WHO Lifetime Version 2.1), which
189 establishes diagnoses according to DSM-IV criteria (Hardeveld et al., 2013). Depression severity was

determined using the 30-item Inventory of Depressive Symptoms Self-Report Questionnaire (IDS-SR_{30}) (Rush et al., 1996). For the present study, we analysed 217 NESDA individuals with a current diagnosis of MDD (six-month recency) who initiated treatment with an antidepressant (could be from multiple classes) during the two year follow-up period and, who at year two (Ty2), were still on antidepressant use. Patients who had no overnight fast before baseline blood draw and women who were pregnant or over 32 days since last menstruation were not included in this sample. Patients that were on lengthy (over 2 months) antidepressant use already at baseline were also excluded in order to focus on persons who were antidepressant free or only recently initiated antidepressant use.

Definitions of treatment response

Treatment response was defined as at least 50% reduction in HAMD sum scores from baseline to endpoint (weeks 4-26) for cohorts 1-4 and, at least 50% reduction in IDS sum scores from baseline to endpoint (year two) for cohort 5.

Serum preparation and multiplex immunoassay

Standard operating protocols were followed for serum sample preparation across all clinical centres, as described previously (Chan et al., 2015b). The Multi-Analyte Profiling immunoassay platform (DiscoveryMAP) was used to measure the concentrations of 258 (cohort 1), 256 (cohort 2), 190 (cohort 3), 147 (cohort 4) and 243 (cohort 5) proteins in patient sera. The number of proteins measured in each cohort was different because different upgrade versions of the DiscoveryMAP platforms were used over time, each measuring slightly different proteins. The proteins measured were mainly involved in immune/inflammatory, endocrine and metabolic processes previously implicated in several psychiatric disorders including depression (Bot et al., 2015; Chan et al., 2015b; Haenisch et al., 2014). All assays were conducted in the Clinical Laboratory Improved Amendments (CLIA)–certified laboratory at Myriad-RBM (Austin, TX, USA) (described previously (Chan et al., 2015b)). All serum samples were stored at -80°C until analysis.

Statistical analysis

All statistical analyses were performed in R (http://www.R-project.org/) (RCoreTeam, 2013). Data from all cohorts were quality control (QC) assessed and pre-processed to exclude proteins with greater than 30% missing values (QC criteria), as described previously (Chan et al., 2015b). The remaining data with values below or above the detection limits were imputed by the minimum and maximum detected values, respectively. Data were $\log_{10}$-transformed to stabilise variance and approximate normality. Sample outliers were examined using principal components analysis (PCA) (Barnett and Lewis, 1978) and through inspection of quantile-quantile (Q-Q) plots. Linear regression analyses were carried out to identify biomarkers associated with treatment response. For each regression model, the pre-treatment protein levels were individually included as predictor variables and the absolute change in depression scores (absolute change in HAMD scores (ΔHAMD) for cohorts 1-4 and IDS scores (ΔIDS) for cohort 5) was modelled as the continuous outcome variable. This was done for each cohort. Covariate adjustment was accomplished through forward and backward stepwise regression, with selection based upon Bayesian Information Criterion (BIC). For cohorts 1-4, the clinical and sociodemographic covariates adjusted for included baseline HAMD scores, age, gender and BMI. For cohort 5, a larger set of sociodemographic covariates were available for adjustment including baseline IDS scores, age, gender, BMI, anxiety diagnosis comorbidity, chronic diseases and somatic medication **(Table 1)**. Regression diagnostics were examined to ensure that all the model assumptions were met. False discovery rate was controlled according to Benjamini and Hochberg (Benjamini and Hochberg, 1995). However, given that this was an exploratory study, unadjusted P-values of less than 0.05 were considered to be worth further study. Biological and molecular functions were assigned using Swissprot (UniProt, 2015).

Results

Patient characteristics and treatment response rates

The baseline patient characteristics are described in **Table 1**. Briefly, patients from cohorts 1 and 2 were on average 10 years older than patients from cohorts 3-5. While cohort 1 had an equal proportion of male and female patients with an average BMI of 23, the remaining cohorts had more females (58-67%) and a higher BMI of 25-26. Contrary to cohorts 1-4, patients who were either drug-naive or antidepressant medication free for one or six weeks, approximately 79% of cohort 5 patients were receiving antidepressants at baseline for less than two months. In addition, unlike cohort 1-4 patients who were recruited from specialised mental healthcare, cohort 5 patients were from the general population (7%), primary care (26%) and specialised mental healthcare (67%). Finally, approximately 71% of patients from cohort 5 also had a comorbid anxiety diagnosis, which was not the case for cohorts 1-4. The treatment response rates varied across the cohorts. High response rates of over 84% to 4-26 weeks treatment with mixed antidepressants were observed for drug-naive or medication free patients from cohorts 3 and 4. While response to seven weeks of treatment with Venlafaxine (cohort 1) was 63%, treatment with Imipramine (cohort 2) only resulted in a 27% response. Similarly, longer-term treatment of up to two years with mixed antidepressants in cohort 5 also only resulted in a response rate of 29%.

Multiplex immunoassay data QC and pre-processing

Approximately 16-30% of proteins failed QC (i.e. >30% missing values) across the five cohorts. The number of proteins left for analysis in each cohort was 218 (cohort 1), 211 (cohort 2), 150 (cohort 3), 115 (cohort 4) and 171 (cohort 5) **(Supplementary Table 1)**. In total, 78 (31%) proteins were measured in all five cohorts, 54 (22%) in any four cohorts, 56 (23%) in any three cohorts, 31 (12%) in any two cohorts and 29 (12%) in only one cohort.

Biomarkers associated with antidepressant treatment response

The biomarkers associated with antidepressant treatment response identified were predominantly involved in immune/inflammatory processes and blood coagulation followed by endocrine and growth factor signalling **(Table 2 and Supplementary Table 2).** A total of 11 baseline proteins were associated with response to Venlafaxine treatment (cohort 1). Of these, nine were negatively (-β) associated with response (i.e. a lower pre-treatment protein level is associated with better response) and two were positively (β) associated with response (i.e. a higher pre-treatment protein level is associated with better response). Twenty-five proteins were associated with response to Imipramine (cohort 2) including 12 negative and 13 positive associations. While 19 (four negative and 15 positive) proteins were associated with response to six weeks of treatment with mixed antidepressants (cohort 3), another 23 (10 negative and 13 positive) were associated with response to 4-26 weeks of treatment with mixed antidepressants (cohort 4). Tissue Inhibitor of Metalloproteinases 1 (TIMP-1) and Intercellular Adhesion Molecule 1 (ICAM-1) along with two acute phase proteins, Plasminogen Activator Inhibitor 1 (PAI-1) and Thrombopoietin (TPO), were the four biomarkers of treatment response in common between these two cohorts. Finally, a total of 12 proteins were associated with response to longer-term treatment of two years with mixed antidepressants in the naturalistic NESDA cohort 5, including nine negative and three positive associations.

Notably, the proteins associated with response to the different antidepressant treatments across the various cohorts were largely different or potentially antidepressant specific with only nine proteins in common in at least two out of the five cohorts. These proteins included Apolipoprotein A-IV (ApoA-IV), Endoglin, ICAM-1, PAI-1, TIMP-1, TPO, Complement C3 (C3), Hepatocyte Growth Factor (HGF) and Insulin-like Growth Factor-Binding Protein 2 (IGFBP-2) **(Table 2)**. ApoA-IV was the most reproducible biomarker of treatment response as it was significantly associated with response to treatment in three out of five cohorts. Lower pre-treatment ApoA-IV levels were associated with better response to seven weeks of treatment with Venlafaxine (β=-26.47, p=0.001) and six weeks with mixed antidepressants (cohort 3: β=-8.24, p=0.029) but poorer response to a longer-term treatment with mixed antidepressants in the naturalistic cohort 5 (β=9.39, p=0.027) **(Figure 1).** Endoglin, also known as CD105, was another notable biomarker of treatment response. While it was only measured in three cohorts (1, 2 and 5), it associated

with response to treatment in all three cohorts. For instance, lower pre-treatment levels were associated with better response to treatment with Venlafaxine (β=-22.61, p=0.035) and Imipramine (β=-34.56, p=0.011), respectively, but poorer response to longer-term treatment with mixed antidepressants in cohort 5 (β=22.89, p=0.004). ICAM-1 was also associated with response to antidepressant treatment in three cohorts. Higher pre-treatment levels were associated with better response to mixed antidepressants in both cohorts 3 (β=22.31, p=0.001) and 4 (β=20.37, p=0.001) but poorer response to Venlafaxine treatment (β=-21.08, p=0.035) **(Figure 1).** The remaining six proteins were also associated with response to several treatments. For example, higher pre-treatment levels of the three blood coagulation proteins, PAI-1, TIMP-1 and TPO, were associated with better response to mixed antidepressant treatment in both cohorts 3 and 4. On the other hand, the immune/inflammatory protein, C3, and the growth factor signalling proteins, HGF and IGFBP-2, were associated with response to Imipramine and mixed antidepressants (cohorts 3 or 4), inversely **(Figure 1).**

Validation the ApoA-IV findings by liquid-chromatography mass spectrometry (LC–MS^E)

Of the nine candidate biomarkers of treatment response described above, two including ApoA-IV and Endoglin were not measured in cohort 4 due to use of an older version of the DiscoveryMAP. In order to validate these results, we examined LC–MS^E data from an unpublished study measuring over 400 proteins in serum from 25 MDD patients (mean age (44 years) and gender (7 males, 18 females)). Seventeen of which were also part of our cohort 4. For details of the LC–MS^E approach see **Supplementary Material.** We found that Endoglin was not measurable by LC–MS^E but ApoA-IV was and its pre-treatment levels were indeed significantly associated with response to 4-26 weeks of mixed antidepressant treatment (β=-15.60, p=0.034), validating the results from the other three cohorts **(Figure 1).**

Discussion

Promising candidate biomarkers of treatment response have emerged from recent studies. In the present study, we extended these findings by profiling up to 258 pre-treatment immune/inflammatory, endocrine and metabolic serum proteins from 332 MDD patients recruited from multiple independent clinical centres.

Firstly, we found that nine proteins, ApoA-IV, Endoglin, ICAM-1, PAI-1, TIMP-1, TPO, C3, HGF and IGFBP-2, were significantly associated with response to several antidepressants. Although validation is warranted, this finding supported a potential role of such biomarkers in treatment response. Equally, this finding also suggested a "generic" role of ApoA-IV in treatment response independent of drug or drug class **(Figure 1 and Table 2)**. Secondly, we showed that a distinct and specific set of immune-endocrine proteins were significantly associated with response to certain classes of antidepressants or indeed specific antidepressant drugs. This implied that in the future it may be possible to match the appropriate medication to a given patient based on their pre-treatment immune-endocrine profile. The fact that most of the biomarkers of treatment response identified have previously been implicated in depression further reinforces their role in treatment response (**Table 2** for supporting literature references). Importantly, despite the need for further validation, our findings may represent the first preliminary steps towards establishing robust treatment response predictors, providing hope for future personalised treatment approaches (**Figure 1**).

The strength of our study was that we investigated patients (cohorts 1-4) who were free of major chronic illnesses and somatic medications as well as drug-naive or medication free prior to baseline assessment and blood collection. These factors typically affect blood protein levels and some of the chronic illnesses are known to be linked with a greater risk to develop depression (Haddad et al., 2015). Treatment with antidepressant monotherapies (Venlafaxine and Imipramine) was also a strength of this study, as it enables identification of drug-specific biomarkers of treatment response. In the naturalistic cohort 5, we also statistically adjusted for these confounding factors in our regression models.

ApoA-IV is a circulating lipoprotein that regulates lipid absorption, transport and metabolism and, controls satiety (Stan et al., 2003). This protein has been reported to be increased in MDD (Bot et al., 2015)

and post-stroke depression patients (Zhan et al., 2014) and, has recently been included in a panel of biomarkers used to discriminate older adults with and without depressive symptoms (Arnold et al., 2012). Nevertheless, circulating ApoA-IV has not been previously associated with treatment response in MDD patients. We showed that patients with lower pre-treatment ApoA-IV levels responded better to treatment with Venlafaxine and mixed antidepressants in both cohorts 3 and 4. However, patients from the naturalistic NESDA cohort 5 with lower ApoA-IV levels had poorer responses to longer-term treatment of up to two years with mixed antidepressants. Note that there are fundamental differences between this and the shorter-term treatment cohorts 1-4. Given the naturalistic and non-interventional nature of cohort 5, medication compliance was not monitored during the two years of treatment and was only based on self-reports; most patients had a comorbid anxiety diagnosis, which can affect treatment efficacy (Fava et al., 2008); and, patients were not excluded on the basis of having comorbid chronic illnesses or taking somatic medications, although such variables were included as covariates in the backward and forward stepwise regression analysis.

Endoglin is involved in vascular regulation and angiogenesis, induces inflammation and release of angiogenic factors from inflammatory cells (Nassiri et al., 2011). This protein has not been previously implicated in depression or associated with antidepressant treatment response. In our study, Endoglin was not measured in two cohorts but it was significantly associated with response to treatment in all the cohorts where it was measured. Patients with lower pre-treatment Endoglin levels responded better to both Venlafaxine and Imipramine monotherapies but had poorer responses to longer-term treatment with mixed antidepressants in the NESDA cohort.

ICAM-1 is an immunoglobulin (Ig)-like cell-adhesion receptor that is involved in leukocyte adhesion and movement across the endothelium during inflammation. Expression is regulated by pro-inflammatory cytokines and stress (Mruk et al., 2014). ICAM-1 has been reported to be increased in both serum (Dimopoulos et al., 2006; Lesperance et al., 2004) and post-mortem brain tissue from depression patients (Thomas et al., 2000). We found that patients with higher pre-treatment ICAM-1 levels responded better to mixed antidepressants in cohorts 3 and 4 but had poorer responses to Venlafaxine treatment (**Figure 1**).

The remaining seven proteins that were associated with response to several antidepressants have all been previously implicated in depression. For example, the blood coagulation and positive acute phase (+AP) proteins, PAI-1, TIMP-1 and TPO have been shown to be increased in MDD patients (Domenici et al., 2010; Eskandari et al., 2005; Gorska-Ciebiada et al., 2016; Tsai et al., 2008). Genetic variants of the PAI-1 gene have been linked to depression as well as antidepressant treatment response (Tsai et al., 2008). In our study, patients from cohorts 3 and 4 with higher pre-treatment levels of these three proteins responded better to mixed antidepressants. The immune/inflammatory protein, C3 (+AP) along with the growth factor signalling proteins, HGF (+AP) and IGFBP-2, were all associated with response to Imipramine and either short or long-term treatment with mixed antidepressants. While C3 and IGFBP-2 have both been found to be increased in MDD (Domenici et al., 2010; Powell et al., 2014), HGF has been reported to be both decreased (Russo, 2010) and increased (Arnold et al., 2012) in patients.

Limitations of the study

The use of different versions of the multiplex immunoassay platform and difficulty to reliably measure over 250 proteins covering a wide protein concentration range was a notable limitation of our study. Protein exclusion rate due to QC failure ranged between 16% and 30%. The overlap of proteins measured across all five cohorts was only 31%, followed by 22% in any four, 23% in any three and 12% in any two cohorts. This limitation directly compromises assessment of reproducibility of some of the candidate biomarkers of treatment response including, for example, Endoglin and some of the other biomarkers identified in only one cohort **(Table 2)**. Also as a result, some of the previously reported treatment related proteins such as IL-6, S100-B, IL-1β and IFN-γ (Janssen et al., 2010) could not be fully assessed. Consequently, future work attempting to improve consistency and reliability of protein measurement is warranted. On the other hand, we did reliably measure BDNF and TNF-α, two of the most commonly studied candidate biomarkers of treatment response (Mikoteit et al., 2014; Papakostas, 2012), but were not able to reproduce the reported findings in our study. We also acknowledge the fact that despite promising, some of our findings were in opposite directions across cohorts and failed to project to the naturalistic cohort. For instance, while the ApoA-IV and Endoglin associations with treatment response were consistent across the smaller shorter-

term treatment cohorts, the effects were in opposite direction in the larger naturalistic but fundamentally different longer-term treatment cohort 5. Similarly, opposite directions of association between ICAM-1, C3, HGF and IGFBP-2 and treatment response were observed across the venlafaxine or imipramine monotherapy cohorts (cohorts 1 and 2) and the mixed antidepressant treatment cohorts (cohorts 3 and 4). While these results could suggest that these proteins may play a role in treatment response depending on the class or specific antidepressant drug, the presence of inconsistencies across some of the key findings highlight the need for validation studies. The disagreement of results with the literature and importantly, within our own study may be explained by the heterogeneity of the patient population characterised by sociodemographic, lifestyle and clinical factors, disease comorbidities and concomitant medications. Differences in sample sizes and duration of treatment, variety of antidepressant medications administered, the heterogeneity of the concept "depression" and whether the original diagnosis of MDD was correct i.e. misdiagnosis of bipolar disorder in depressive phase, may also explain some of the inconsistencies, which altogether challenge the comparison of findings across cohorts. Finally, we acknowledge the fact that our findings are at very preliminary stages and are not immediately useful to every-day clinical practice.

In summary, we demonstrated for the first time that circulating ApoA-IV, Endoglin, ICAM-1, PAI-1, TIMP-1, TPO, C3, HGF and IGFBP-2 were associated with response to some antidepressant drugs and, that specific sets of immune-endocrine proteins were associated with response to certain classes or individual antidepressant drugs. These preliminary findings may represent early steps towards future personalised treatment approaches.

References

Abou-Saleh, M.T., Ghubash, R., Karim, L., Krymski, M., Bhai, I., 1998. Hormonal aspects of postpartum depression. Psychoneuroendocrinology 23(5), 465-475.

API, 2000. Diagnostic and statistical manual of mental disorders DSM-IV-TR. 4th ed. American Psychiatric Association, Arlington, VA.

Arnold, S.E., Xie, S.X., Leung, Y.Y., Wang, L.S., Kling, M.A., Han, X., Kim, E.J., Wolk, D.A., Bennett, D.A., Chen-Plotkin, A., Grossman, M., Hu, W., Lee, V.M., Mackin, R.S., Trojanowski, J.Q., Wilson, R.S., Shaw, L.M., 2012. Plasma biomarkers of depressive symptoms in older adults. Transl Psychiatry 2, e65.

Bai, Y.M., Chiou, W.F., Su, T.P., Li, C.T., Chen, M.H., 2014. Pro-inflammatory cytokine associated with somatic and pain symptoms in depression. J Affect Disord 155, 28-34.

Barnett, V., Lewis, T., 1978. *Outliers in Statistical Data*. John Wiley & Sons, Inc. , New York.

Baune, B.T., Neuhauser, H., Ellert, U., Berger, K., 2010. The role of the inflammatory markers ferritin, transferrin and fibrinogen in the relationship between major depression and cardiovascular disorders - The German Health Interview and Examination Survey. Acta Psychiatr Scand 121(2), 135-142.

Benjamini, Y., Hochberg, Y., 1995. Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. Journal of the Royal Statistical Society. Series B (Methodological) 57(1), 289-300.

Berk, M., Williams, L.J., Jacka, F.N., O'Neil, A., Pasco, J.A., Moylan, S., Allen, N.B., Stuart, A.L., Hayley, A.C., Byrne, M.L., Maes, M., 2013. So depression is an inflammatory disease, but where does the inflammation come from? BMC Med 11, 200.

Bossuyt, P.M., Reitsma, J.B., Bruns, D.E., Gatsonis, C.A., Glasziou, P.P., Irwig, L.M., Lijmer, J.G., Moher, D., Rennie, D., de Vet, H.C., 2003. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. The Standards for Reporting of Diagnostic Accuracy Group. Croat Med J 44(5), 635-638.

Bot, M., Chan, M.K., Jansen, R., Lamers, F., Vogelzangs, N., Steiner, J., Leweke, F.M., Rothermundt, M., Cooper, J., Bahn, S., Penninx, B.W., 2015. Serum proteomic profiling of major depressive disorder. Transl Psychiatry 5, e599.

Carvalho, A.F., Rocha, D.Q., McIntyre, R.S., Mesquita, L.M., Kohler, C.A., Hyphantis, T.N., Sales, P.M., Machado-Vieira, R., Berk, M., 2014. Adipokines as emerging depression biomarkers: a systematic review and meta-analysis. J Psychiatr Res 59, 28-37.

Cattaneo, A., Ferrari, C., Uher, R., Bocchio-Chiavetto, L., Riva, M.A., Consortium, M.R.C.I., Pariante, C.M., 2016. Absolute Measurements of Macrophage Migration Inhibitory Factor and Interleukin-1-beta mRNA Levels Accurately Predict Treatment Response in Depressed Patients. Int J Neuropsychopharmacol doi: 10.1093/ijnp/pyw045.

Chan, M.K., Cooper, J.D., Bot, M., Steiner, J., Penninx, B.W., Bahn, S., 2015a. Identification of an Immune-Neuroendocrine Biomarker Panel for Detection of Depression: A Joint Effects Statistical Approach. Neuroendocrinology DOI: 10.1159/000442208.

Chan, M.K., Gottschalk, M.G., Haenisch, F., Tomasik, J., Ruland, T., Rahmoune, H., Guest, P.C., Bahn, S., 2014. Applications of blood-based protein biomarker strategies in the study of psychiatric disorders. Prog Neurobiol 122, 45-72.

Chan, M.K., Krebs, M.O., Cox, D., Guest, P.C., Yolken, R.H., Rahmoune, H., Rothermundt, M., Steiner, J., Leweke, F.M., van Beveren, N.J., Niebuhr, D.W., Weber, N.S., Cowan, D.N., Suarez-Pinilla, P., Crespo-Facorro, B., Mam-Lam-Fook, C., Bourgin, J., Wenstrup, R.J., Kaldate, R.R., Cooper, J.D., Bahn, S., 2015b. Development of a blood-based molecular biomarker test for identification of schizophrenia before disease onset. Transl Psychiatry 5, e601.

Cubala, W.J., Landowski, J., 2014. C-reactive protein and cortisol in drug-naive patients with short-illness-duration first episode major depressive disorder: possible role of cortisol immunomodulatory action at early stage of the disease. J Affect Disord 152-154, 534-537.

Deuschle, M., Blum, W.F., Strasburger, C.J., Schweiger, U., Weber, B., Korner, A., Standhardt, H., Gotthardt, U., Schmider, J., Pflaum, C.D., Heuser, I., 1997. Insulin-like growth factor-I (IGF-I) plasma concentrations are increased in depressed patients. Psychoneuroendocrinology 22(7), 493-503.

Dimopoulos, N., Piperi, C., Salonicioti, A., Mitsonis, C., Liappas, I., Lea, R.W., Kalofoutis, A., 2006. Elevation of plasma concentration of adhesion molecules in late-life depression. Int J Geriatr Psychiatry 21(10), 965-971.

Ditzen, C., Tang, N., Jastorff, A.M., Teplytska, L., Yassouridis, A., Maccarrone, G., Uhr, M., Bronisch, T., Miller, C.A., Holsboer, F., Turck, C.W., 2012. Cerebrospinal fluid biomarkers for major depression confirm relevance of associated pathophysiology. Neuropsychopharmacology 37(4), 1013-1025.

Domenici, E., Wille, D.R., Tozzi, F., Prokopenko, I., Miller, S., McKeown, A., Brittain, C., Rujescu, D., Giegling, I., Turck, C.W., Holsboer, F., Bullmore, E.T., Middleton, L., Merlo-Pich, E., Alexander, R.C., Muglia, P., 2010. Plasma protein biomarkers for depression and schizophrenia by multi analyte profiling of case-control collections. PLoS One 5(2), e9166.

Ejchel, T.F., Araujo, L.M., Ramos, L.R., Cendoroglo, M.S., de Arruda Cardoso Smith, M., 2005. Association of the apolipoprotein A-IV: 360 Gln/His polymorphism with cerebrovascular disease, obesity, and depression in a Brazilian elderly population. Am J Med Genet B Neuropsychiatr Genet 135B(1), 65-68.

Emanuele, E., Martinelli, V., Carlin, M.V., Fugazza, E., Barale, F., Politi, P., 2011. Serum levels of soluble receptor for advanced glycation endproducts (sRAGE) in patients with different psychiatric disorders. Neurosci Lett 487(1), 99-102.

Eskandari, F., Mistry, S., Martinez, P.E., Torvik, S., Kotila, C., Sebring, N., Drinkard, B.E., Levy, C., Reynolds, J.C., Csako, G., Gold, P.W., Horne, M., Cizza, G., Group, P.S., 2005. Younger, premenopausal women with major depressive disorder have more abdominal fat and increased serum levels of prothrombotic factors: implications for greater cardiovascular risk. Metabolism 54(7), 918-924.

Fava, M., Rush, A.J., Alpert, J.E., Balasubramani, G.K., Wisniewski, S.R., Carmin, C.N., Biggs, M.M., Zisook, S., Leuchter, A., Howland, R., Warden, D., Trivedi, M.H., 2008. Difference in treatment outcome in outpatients with anxious versus nonanxious depression: a STAR*D report. Am J Psychiatry 165(3), 342-351.

Gimenez-Palop, O., Coronas, R., Cobo, J., Gallart, L., Barbero, J.D., Parra, I., Fuste, G., Vendrell, J., Bueno, M., Gonzalez-Clemente, J.M., Caixas, A., 2012. Fasting plasma peptide YY concentrations are increased in patients with major depression who associate weight loss. J Endocrinol Invest 35(7), 645-648.

Gold, P.W., Pavlatou, M.G., Carlson, P.J., Luckenbaugh, D.A., Costello, R., Bonne, O., Csako, G., Drevets, W.C., Remaley, A.T., Charney, D.S., Neumeister, A., Kling, M.A., 2012. Unmedicated, remitted patients with major depression have decreased serum immunoglobulin A. Neurosci Lett 520(1), 1-5.

Gorska-Ciebiada, M., Saryusz-Wolska, M., Borkowska, A., Ciebiada, M., Loba, J., 2016. Plasma levels of thrombomodulin, plasminogen activator inhibitor-1 and fibrinogen in elderly, diabetic patients with depressive symptoms. Aging clinical and experimental research 28(5), 843-851.

Grosse, L., Carvalho, L.A., Birkenhager, T.K., Hoogendijk, W.J., Kushner, S.A., Drexhage, H.A., Bergink, V., 2016. Circulating cytotoxic T cells and natural killer cells as potential predictors for antidepressant response in melancholic depression. Restoration of T regulatory cell populations after antidepressant therapy. Psychopharmacology (Berl) 233(9), 1679-1688.

Haddad, P.M., Talbot, P.S., Anderson, I.M., McAllister-Williams, R.H., 2015. Managing inadequate antidepressant response in depressive illness. Br Med Bull 115(1), 183-201.

Haenisch, F., Alsaif, M., Guest, P.C., Rahmoune, H., Dickerson, F., Yolken, R., Bahn, S., 2014. Multiplex immunoassay analysis of plasma shows prominent upregulation of growth factor activity pathways linked to GSK3beta signaling in bipolar patients. J Affect Disord 156, 139-143.

Hannestad, J., DellaGioia, N., Bloch, M., 2011. The effect of antidepressant medication treatment on serum levels of inflammatory cytokines: a meta-analysis. Neuropsychopharmacology 36(12), 2452-2459.

Hardeveld, F., Spijker, J., De Graaf, R., Hendriks, S.M., Licht, C.M., Nolen, W.A., Penninx, B.W., Beekman, A.T., 2013. Recurrence of major depressive disorder across different treatment settings: results from the NESDA study. J Affect Disord 147(1-3), 225-231.

Hashimoto, K., 2015. Inflammatory biomarkers as differential predictors of antidepressant response. Int J Mol Sci 16(4), 7796-7801.

Janssen, D.G., Caniato, R.N., Verster, J.C., Baune, B.T., 2010. A psychoneuroimmunological review on cytokines involved in antidepressant treatment response. Hum Psychopharmacol 25(3), 201-215.

Kaestner, F., Hettich, M., Peters, M., Sibrowski, W., Hetzel, G., Ponath, G., Arolt, V., Cassens, U., Rothermundt, M., 2005. Different activation patterns of proinflammatory cytokines in melancholic and non-melancholic major depression are associated with HPA axis activity. J Affect Disord 87(2-3), 305-311.

Karaoulanis, S.E., Rizouli, K.A., Rizoulis, A.A., Angelopoulos, N.V., 2014. Lack of association of acute phase response proteins with hormone levels and antidepressant medication in perimenopausal depression. BMC Psychiatry 14, 164.

514 Karlovic, D., Serretti, A., Vrkic, N., Martinac, M., Marcinko, D., 2012. Serum concentrations of CRP, IL-6, TNF-alpha and cortisol in
515 major depressive disorder with melancholic or atypical features. Psychiatry Res 198(1), 74-80.

516 Keitner, G.I., Ryan, C.E., Miller, I.W., Norman, W.H., 1992. Recovery and major depression: factors associated with twelve-month
517 outcome. Am J Psychiatry 149(1), 93-99.

518 Lehto, S.M., Niskanen, L., Miettola, J., Tolmunen, T., Viinamaki, H., Mantyselka, P., 2010. Serum anti-inflammatory markers in
519 general population subjects with elevated depressive symptoms. Neurosci Lett 484(3), 201-205.

520 Lesperance, F., Frasure-Smith, N., Theroux, P., Irwin, M., 2004. The association between major depression and levels of soluble
521 intercellular adhesion molecule 1, interleukin-6, and C-reactive protein in patients with recent acute coronary syndromes. Am J
522 Psychiatry 161(2), 271-277.

523 Leuchter, A.F., Cook, I.A., Hunter, A.M., Korb, A.S., 2009. A new paradigm for the prediction of antidepressant treatment response.
524 Dialogues Clin Neurosci 11(4), 435-446.

525 Lu, S., Peng, H., Wang, L., Vasish, S., Zhang, Y., Gao, W., Wu, W., Liao, M., Wang, M., Tang, H., Li, W., Li, W., Li, Z., Zhou, J., Zhang, Z.,
526 Li, L., 2013. Elevated specific peripheral cytokines found in major depressive disorder patients with childhood trauma exposure: a
527 cytokine antibody array analysis. Compr Psychiatry 54(7), 953-961.

528 Maes, M., Bosmans, E., De Jongh, R., Kenis, G., Vandoolaeghe, E., Neels, H., 1997. Increased serum IL-6 and IL-1 receptor antagonist
529 concentrations in major depression and treatment resistant depression. Cytokine 9(11), 853-858.

530 Maes, M., Scharpe, S., Bosmans, E., Vandewoude, M., Suy, E., Uyttenbroeck, W., Cooreman, W., Vandervorst, C., Raus, J., 1992.
531 Disturbances in acute phase plasma proteins during melancholia: additional evidence for the presence of an inflammatory process
532 during that illness. Prog Neuropsychopharmacol Biol Psychiatry 16(4), 501-515.

533 Maes, M., Song, C., Lin, A.H., Bonaccorso, S., Kenis, G., De Jongh, R., Bosmans, E., Scharpe, S., 1999. Negative immunoregulatory
534 effects of antidepressants: inhibition of interferon-gamma and stimulation of interleukin-10 secretion. Neuropsychopharmacology
535 20(4), 370-379.

536 Mikoteit, T., Beck, J., Eckert, A., Hemmeter, U., Brand, S., Bischof, R., Holsboer-Trachsler, E., Delini-Stula, A., 2014. High baseline
537 BDNF serum levels and early psychopathological improvement are predictive of treatment outcome in major depression.
538 Psychopharmacology (Berl) 231(15), 2955-2965.

539 Miller, D.B., O'Callaghan, J.P., 2013. Personalized medicine in major depressive disorder -- opportunities and pitfalls. Metabolism 62
540 Suppl 1, S34-39.

541 Mruk, D.D., Xiao, X., Lydka, M., Li, M.W., Bilinska, B., Cheng, C.Y., 2014. Intercellular adhesion molecule 1: recent findings and new
542 concepts involved in mammalian spermatogenesis. Seminars in cell & developmental biology 29, 43-54.

543 Nassiri, F., Cusimano, M.D., Scheithauer, B.W., Rotondo, F., Fazio, A., Yousef, G.M., Syro, L.V., Kovacs, K., Lloyd, R.V., 2011. Endoglin
544 (CD105): a review of its role in angiogenesis and tumor diagnosis, progression and therapy. Anticancer research 31(6), 2283-2290.

545 Neubauer, H., Petrak, F., Zahn, D., Pepinghege, F., Hagele, A.K., Pirkl, P.A., Uhl, I., Juckel, G., Mugge, A., Herpertz, S., 2013. Newly
546 diagnosed depression is associated with increased beta-thromboglobulin levels and increased expression of platelet activation
547 markers and platelet derived CD40-CD40L. J Psychiatr Res 47(7), 865-871.

548 NICE, 2010. Depression: The Treatment and Management of Depression in Adults (Updated Edition). Leicester (UK).

549 Okamura, F., Tashiro, A., Utumi, A., Imai, T., Suchi, T., Tamura, D., Sato, Y., Suzuki, S., Hongo, M., 2000. Insulin resistance in patients
550 with depression and its changes during the clinical course of depression: minimal model analysis. Metabolism 49(10), 1255-1260.

551 Olfson, M., Marcus, S.C., Tedeschi, M., Wan, G.J., 2006. Continuity of antidepressant treatment for adults with depression in the
552 United States. Am J Psychiatry 163(1), 101-108.

553 Owens, M., Herbert, J., Jones, P.B., Sahakian, B.J., Wilkinson, P.O., Dunn, V.J., Croudace, T.J., Goodyer, I.M., 2014. Elevated morning
554 cortisol is a stratified population-level biomarker for major depression in boys only with high depressive symptoms. Proc Natl Acad
555 Sci U S A 111(9), 3638-3643.

556 Papakostas, G.I., 2012. Surrogate markers of treatment outcome in major depressive disorder. Int J Neuropsychopharmacol 15(6),
557 841-854.

Papakostas, G.I., Fava, M., 2009. Does the probability of receiving placebo influence clinical trial outcome? A meta-regression of double-blind, randomized clinical trials in MDD. Eur Neuropsychopharmacol 19(1), 34-40.

Papakostas, G.I., Shelton, R.C., Kinrys, G., Henry, M.E., Bakow, B.R., Lipkin, S.H., Pi, B., Thurmond, L., Bilello, J.A., 2013. Assessment of a multi-assay, serum-based biological diagnostic test for major depressive disorder: a pilot and replication study. Mol Psychiatry 18(3), 332-339.

Penninx, B.W., Beekman, A.T., Smit, J.H., Zitman, F.G., Nolen, W.A., Spinhoven, P., Cuijpers, P., De Jong, P.J., Van Marwijk, H.W., Assendelft, W.J., Van Der Meer, K., Verhaak, P., Wensing, M., De Graaf, R., Hoogendijk, W.J., Ormel, J., Van Dyck, R., 2008. The Netherlands Study of Depression and Anxiety (NESDA): rationale, objectives and methods. Int J Methods Psychiatr Res 17(3), 121-140.

Phillips, M.L., Chase, H.W., Sheline, Y.I., Etkin, A., Almeida, J.R., Deckersbach, T., Trivedi, M.H., 2015. Identifying predictors, moderators, and mediators of antidepressant response in major depressive disorder: neuroimaging approaches. Am J Psychiatry 172(2), 124-138.

Powell, T.R., McGuffin, P., D'Souza, U.M., Cohen-Woods, S., Hosang, G.M., Martin, C., Matthews, K., Day, R.K., Farmer, A.E., Tansey, K.E., Schalkwyk, L.C., 2014. Putative transcriptomic biomarkers in the inflammatory cytokine pathway differentiate major depressive disorder patients from control subjects and bipolar disorder patients. PLoS One 9(3), e91076.

RCoreTeam, 2013. R: A language and environment for statistical computing. R Foundation for Statistical Computing. Vienna, Austria. http://www.R-project.org/.

Rhebergen, D., Korten, N.C., Penninx, B.W., Stek, M.L., van der Mast, R.C., Oude Voshaar, R., Comijs, H.C., 2015. Hypothalamic-pituitary-adrenal axis activity in older persons with and without a depressive disorder. Psychoneuroendocrinology 51, 341-350.

Rothermundt, M., Arolt, V., Peters, M., Gutbrodt, H., Fenker, J., Kersting, A., Kirchner, H., 2001. Inflammatory markers in major depression and melancholia. J Affect Disord 63(1-3), 93-102.

Rush, A.J., Gullion, C.M., Basco, M.R., Jarrett, R.B., Trivedi, M.H., 1996. The Inventory of Depressive Symptomatology (IDS): psychometric properties. Psychol Med 26(3), 477-486.

Rush, A.J., Warden, D., Wisniewski, S.R., Fava, M., Trivedi, M.H., Gaynes, B.N., Nierenberg, A.A., 2009. STAR*D: revising conventional wisdom. CNS Drugs 23(8), 627-647.

Russo, A.J., 2010. Decreased Serum Hepatocyte Growth Factor (HGF) in Individuals with Depression Correlates with Severity of Disease. Biomark Insights 5, 63-67.

Seidel, A., Arolt, V., Hunstiger, M., Rink, L., Behnisch, A., Kirchner, H., 1995. Cytokine production and serum proteins in depression. Scandinavian journal of immunology 41(6), 534-538.

Simic, I., Maric, N.P., Mitic, M., Soldatovic, I., Pavlovic, Z., Mihaljevic, M., Andric, S., Radojcic, M.B., Adzic, M., 2013. Phosphorylation of leukocyte glucocorticoid receptor in patients with current episode of major depressive disorder. Prog Neuropsychopharmacol Biol Psychiatry 40, 281-285.

Simon, N.M., McNamara, K., Chow, C.W., Maser, R.S., Papakostas, G.I., Pollack, M.H., Nierenberg, A.A., Fava, M., Wong, K.K., 2008. A detailed examination of cytokine abnormalities in Major Depressive Disorder. Eur Neuropsychopharmacol 18(3), 230-233.

Stan, S., Delvin, E., Lambert, M., Seidman, E., Levy, E., 2003. Apo A-IV: an update on regulation and physiologic functions. Biochim Biophys Acta 1631(2), 177-187.

Stelzhammer, V., Haenisch, F., Chan, M.K., Cooper, J.D., Steiner, J., Steeb, H., Martins-de-Souza, D., Rahmoune, H., Guest, P.C., Bahn, S., 2014. Proteomic changes in serum of first onset, antidepressant drug-naive major depression patients. Int J Neuropsychopharmacol 17(10), 1599-1608.

Stetler, C., Miller, G.E., 2011. Depression and hypothalamic-pituitary-adrenal activation: a quantitative summary of four decades of research. Psychosom Med 73(2), 114-126.

Suehs BT AT, Bendele SD, Crismon ML, Trivedi MH, B, K., 2008. Texas Medication Algorithm Project Procedural Manual: Major Depressive Disorder Algorithms. Austin, TX: Texas Department of State Health Services.

Taylor, D., Paton, C., Kapur, S., 2015. The Maudsley Prescribing Guidelines in Psychiatry. Wiley.

Thomas, A.J., Ferrier, I.N., Kalaria, R.N., Woodward, S.A., Ballard, C., Oakley, A., Perry, R.H., O'Brien, J.T., 2000. Elevation in late-life depression of intercellular adhesion molecule-1 expression in the dorsolateral prefrontal cortex. Am J Psychiatry 157(10), 1682-1684.

Tsai, S.J., Hong, C.J., Liou, Y.J., Yu, Y.W., Chen, T.J., 2008. Plasminogen activator inhibitor-1 gene is associated with major depression and antidepressant treatment response. Pharmacogenet Genomics 18(10), 869-875.

Udina, M., Castellvi, P., Moreno-Espana, J., Navines, R., Valdes, M., Forns, X., Langohr, K., Sola, R., Vieta, E., Martin-Santos, R., 2012. Interferon-induced depression in chronic hepatitis C: a systematic review and meta-analysis. J Clin Psychiatry 73(8), 1128-1138.

Uher, R., Tansey, K.E., Dew, T., Maier, W., Mors, O., Hauser, J., Dernovsek, M.Z., Henigsberg, N., Souery, D., Farmer, A., McGuffin, P., 2014. An inflammatory biomarker as a differential predictor of outcome of depression treatment with escitalopram and nortriptyline. Am J Psychiatry 171(12), 1278-1286.

UniProt, C., 2015. UniProt: a hub for protein information. Nucleic acids research 43(Database issue), D204-212.

Vermeiden, M., Mulder, P.G., van den Broek, W.W., Bruijn, J.A., Birkenhager, T.K., 2013. A double-blind randomized study comparing plasma level-targeted dose imipramine and high-dose venlafaxine in depressed inpatients. J Psychiatr Res 47(10), 1337-1342.

Weber-Hamann, B., Blum, W.F., Kratzsch, J., Gilles, M., Heuser, I., Deuschle, M., 2009. Insulin-like growth factor-I (IGF-I) serum concentrations in depressed patients: relationship to saliva cortisol and changes during antidepressant treatment. Pharmacopsychiatry 42(1), 23-28.

Wong, M.L., Kling, M.A., Munson, P.J., Listwak, S., Licinio, J., Prolo, P., Karp, B., McCutcheon, I.E., Geracioti, T.D., Jr., DeBellis, M.D., Rice, K.C., Goldstein, D.S., Veldhuis, J.D., Chrousos, G.P., Oldfield, E.H., McCann, S.M., Gold, P.W., 2000. Pronounced and sustained central hypernoradrenergic function in major depression with melancholic features: relation to hypercortisolism and corticotropin-releasing hormone. Proc Natl Acad Sci U S A 97(1), 325-330.

Zhan, Y., Yang, Y.T., You, H.M., Cao, D., Liu, C.Y., Zhou, C.J., Wang, Z.Y., Bai, S.J., Mu, J., Wu, B., Zhan, Q.L., Xie, P., 2014. Plasma-based proteomics reveals lipid metabolic and immunoregulatory dysregulation in post-stroke depression. Eur Psychiatry 29(5), 307-315.

Tables

Table 1. Patient clinical and sociodemographic characteristics at baseline

a)

	Cohort 1 (n=30)	Cohort 2 (n=26)	Cohort 3 (n=38)	Cohort 4 (n=21)
Numerical variables (mean|median (SD) [min-max])				
Age	54|58 (9) [34-67]	54|56 (11) [32-82]	43|45 (12) [19-59]	42|42 (12) [22-59]
BMI (kg/m^2)	23|23 (3) [15-31]	25|24 (4) [17-33]	26|25 (5) [16-43]	NR
HAMD score	24|24 (3) [18-31]	25|26 (3) [19-30]	22|22 (7) [9-37]	28|29 (5) [21-38]
Follow-up HAMD score	11|10 (8) [1-34]	18|19 (9) [1-36]	7|8 (4) [0-18]	7|7 (3) [0-14]
Categorical variables				
Follow-up time-point	Week 7	Week 7	Week 6	Week 4-26
Response (HAMD reduction ≥50%) by follow-up				
No	11 (37%)	19 (73%)	6 (16%)	1 (5%)
Yes	19 (63%)	7 (27%)	32 (84%)	20 (95%)
Gender				
Female	15 (50%)	17 (65%)	22 (58%)	14 (67%)
Male	15 (50%)	9 (35%)	16 (42%)	7 (33%)
Baseline antidepressant medication				
No*	30 (100%)	26 (100%)	38 (100%)	21 (100%)
Yes	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Follow-up antidepressant class				
No	0 (0%)	0 (0%)	2 (5%)	0 (0%)
SNRI	30 (100%)[#]	0 (0%)	11 (29%)	6 (29%)
TCA	0 (0%)	26 (100%)[†]	1 (3%)	1 (5%)
NaSSA	0 (0%)	0 (0%)	8 (21%)	0 (0%)
SSRI	0 (0%)	0 (0%)	4 (11%)	7 (33%)
Others	0 (0%)	0 (0%)	2 (5%)	7 (33%)
Combination	0 (0%)	0 (0%)	10 (26%)	0 (0%)

NR, Not Recorded; **SNRI,** Serotonin–norepinephrine reuptake inhibitors**; SSRI,** Selective serotonin reuptake inhibitors**; NaSSa,** Noradrenergic and specific serotonergic antidepressants; **TCA,** Tricyclic antidepressants**; BMI,** Body Mass Index; **HAMD,** Hamilton Rating Scale for Depression, 17-item-version; **#,** SNRI (venlafaxine); **†,** TCA (Imipramine); **No***, drug-naive or free for one or six weeks.

b)

	Cohort 5 (n=217)
Numerical variables (mean|median (SD) [min-max])	
Age	42|43 (12) [18-64]
Age of onset	28|25 (13) [5-59]
BMI (kg/m^2)	27|25 (6) [15-53]
Drinks per week	8|1 (14) [0-66]
IDS-SR$_{30}$ score	36|35 (11) [13-63]
Follow-up IDS-SR$_{30}$ score	24|23 (13) [1-61]
Categorical variables	
Follow-up time-point	Year 2
Response (IDS reduction ≥50%) by Year 2	
No	154 (71%)
Yes	63 (29%)
Antidepressant medication at baseline	
No	45 (21%)
Yes	172 (79%)
Follow-up antidepressant medication by Year 2	
No	0 (0%)
SSRI	139 (64%)
Other	40 (18%)
TCA	15 (7%)
SNRI	6 (3%)
NaSSa	3 (1%)
Combination	14 (6%)
Gender	
Female	141 (65%)
Male	76 (35%)
Sampling frame	
General population	16 (7%)
Primary care	56 (26%)
Specialised mental health care	145 (67%)
Chronic diseases	

0	102 (47%)
1 to 2	106 (49%)
Over 3	9 (4%)
MDD Type	
First episode	111 (51%)
Recurrent	106 (49%)
Comorbid anxiety diagnosis	
No	64 (29%)
Yes	153 (71%)
Somatic medications at baseline	
Anti-inflammatory medication	
No	207 (95%)
Yes	10 (5%)
Heart medication	
No	181 (83%)
Yes	36 (17%)
Other psychiatric medications at baseline	
Antipsychotics	
No	204 (94%)
Yes	13 (6%)
Anxiolytics	
No	185 (85%)
Yes	32 (15%)
Benzodiazepines	
No	173 (80%)
Yes	44 (20%)

IDS-SR$_{30}$, Inventory of Depressive Symptoms Self-Report Questionnaire 30-item.

685 **Table 2. Biomarkers of antidepressant treatment response**

Protein	Lit Ref	Func	Cohort 1 (n=30) -Venlafaxine-		Cohort 2 (n=26) -Imipramine-		Cohort 3 (n=38) -Mixed ADs-		Cohort 4 (n=21) -Mixed ADs-		Cohort 5 (n=217) -Mixed ADs-	
			β	P	β	P	β	P	β	P	β	P
B cell-activating factor (BAFF)		IIR	-67.89	0.001	11.15	0.499	---	---	---	---	10.66	0.140
Thrombomodulin (TM)		BC	-41.39	0.012	9.11	0.654	-10.31	0.257	---	---	6.25	0.417
Prostasin	(Bot et al., 2015)	IH	-32.01	0.003	-13.18	0.411	---	---	---	---	3.08	0.514
Pepsinogen I (PGI)		O	-27.00	0.018	11.41	0.267	---	---	---	---	-5.86	0.129
Apolipoprotein A-IV (ApoA-IV)	(Bot et al., 2015; Ejchel et al., 2005; Zhan et al., 2014)	LM	-26.47	0.001	-6.09	0.566	-8.24	0.029	-15.60	0.034*	9.39	0.027
Endoglin		VR	-22.61	0.035	-34.56	0.011	---	---	---	---	22.89	0.004
Intercellular Adhesion Molecule 1 (ICAM-1)	(Dimopoulos et al., 2006; Lesperance et al., 2004; Thomas et al., 2000)	IIR,CA	-21.08	0.035	-24.57	0.097	22.31	0.001	20.37	0.001	1.64	0.799
Eotaxin-1	(Domenici et al., 2010)	IIR	-15.42	0.017	18.02	0.094	3.67	0.231	-4.48	0.118	-4.69	0.142
Receptor for advanced glycosylation end products (RAGE)	(Emanuele et al., 2011)	IIR	-15.08	0.014	-6.49	0.139	1.08	0.600	-2.61	0.439	-2.27	0.447
Vascular endothelial growth factor receptor 3 (VEGFR-3)		GFS,AG	21.19	0.005	-4.44	0.634	---	---	---	---	-0.28	0.949
Interleukin-12 Subunit p40 (IL-12p40)	(Bot et al., 2015; Chan et al., 2015a)	IIR	32.70	0.007	-0.88	0.928	1.93	0.571	---	---	-4.13	0.461
Peptide YY (PYY)	(Gimenez-Palop et al., 2012)	ES,AR	6.01	0.302	-33.80	0.001	---	---	---	---	---	---
Thyroglobulin (TG)		ES,TS	-4.62	0.471	-16.19	0.023	---	---	---	---	-3.64	0.167
Hepatocyte Growth Factor (HGF)	(Arnold et al., 2012; Russo, 2010)	GFS,BC	8.67	0.241	-19.84	0.012	14.86	0.024	-3.03	0.497	-1.35	0.742
Complement C3 (C3)	(Domenici et al., 2010)	IIR,BC	12.11	0.476	-52.06	0.018	-8.02	0.325	15.78	0.024	-0.14	0.985
Latency-Associated Peptide of Transforming Growth Factor beta 1 (LAP TGF-b1)		IIR,BC	4.23	0.788	-50.06	0.025	---	---	---	---	-7.71	0.236
Eosinophil chemotactic protein 2 (Eotaxin-2)	(Powell et al., 2014)	IIR	0.69	0.872	-35.20	6.92E-05	---	---	---	---	-3.86	0.146
Chemokine CC-4 (HCC-4)		IIR	6.34	0.449	-18.56	0.023	1.72	0.649	-0.92	0.780	4.49	0.218
Kallikrein-7 (KLK-7)		IIR	0.22	0.964	-13.91	0.024	---	---	---	---	---	---
Serotransferrin (Transferrin)	(Baune et al., 2010; Maes et al., 1992; Stelzhammer et al., 2014)	IH,BC	-27.31	0.176	-104.6	3.52E-04	-6.00	0.469	---	---	-10.91	0.258
Creatine Kinase-MB (CK-MB)	(Chan et al., 2015a)	IH	-0.86	0.856	-19.57	0.011	-1.05	0.623	2.06	0.539	1.53	0.599
Mesothelin (MSLN)		O	-6.44	0.376	-32.18	0.029	---	---	---	---	3.38	0.392
Matrix Metalloproteinase-1 (MMP-1)		BC	-2.51	0.597	12.54	0.046	1.43	0.680	---	---	-1.84	0.506
Lectin-Like Oxidized LDL Receptor 1 (LOX-1)		BC	-2.31	0.725	15.28	0.049	-2.12	0.562	---	---	-0.59	0.860
Insulin-like Growth Factor-Binding Protein 2 (IGFBP-2)	(Chan et al., 2015a)	GFS	-4.37	0.488	16.07	0.033	4.12	0.170	-6.15	0.027	-2.09	0.514
Vascular Endothelial Growth Factor Receptor 1 (VEGFR-1)		GFS,AG	0.62	0.908	32.18	0.003	---	---	---	---	---	---
Vascular Endothelial Growth Factor C (VEGF-C)		GFS,AG	6.69	0.669	53.20	0.004	---	---	---	---	-10.14	0.199
Interleukin-1 alpha (IL-1 alpha)	(Chan et al., 2015a)	IIR	---	---	20.17	0.042	3.13	0.376	---	---	---	---
Interleukin-15 (IL-15)		IIR	9.18	0.219	20.84	0.008	-2.05	0.323	1.38	0.870	---	---
CD40 Ligand (CD40-L)	(Neubauer et al., 2013)	IIR	3.51	0.531	21.89	0.039	5.05	0.059	-4.74	0.077	1.30	0.565
Resistin	(Carvalho et al., 2014; Papakostas et al., 2013)	IIR,ES	0.14	0.991	33.90	0.041	4.36	0.322	1.14	0.712	-0.04	0.993
Osteoprotegerin (OPG)		IIR	-4.57	0.745	39.80	0.010	---	---	---	---	-8.93	0.138

B Lymphocyte Chemoattractant (BLC)		IIR	5.78	0.491	50.45	0.010	0.66	0.844	-0.89	0.620	---	---
Tamm-Horsfall Urinary Glycoprotein (THP)		IH	3.69	0.697	68.23	1.15E-04	-0.88	0.780	---	---	-0.34	0.942
Apolipoprotein E (Apo E)		LM	-5.51	0.515	36.06	0.011	-0.35	0.935	---	---	4.97	0.110
Fetuin-A	(Bot et al., 2015)	IIR	-16.20	0.281	5.27	0.758	-15.82	0.016	---	---	0.57	0.930
CD5 Antigen-like (CD5L)		IIR	5.77	0.599	-6.95	0.638	-12.63	0.045	---	---	-5.65	0.227
Alpha-2-Macroglobulin (A2Macro)	(Chan et al., 2015a; Ditzen et al., 2012; Domenici et al., 2010; Rothermundt et al., 2001; Seidel et al., 1995)	IIR,BC	6.89	0.693	10.58	0.762	-12.20	0.016	8.52	0.207	-7.16	0.159
Plasminogen Activator Inhibitor 1 (PAI-1)	(Eskandari et al., 2005; Gorska-Ciebiada et al., 2016; Tsai et al., 2008)	BC,AG	11.40	0.385	31.99	0.063	14.60	0.025	20.92	0.001	-2.42	0.665
Tissue Inhibitor of Metalloproteinases 1 (TIMP-1)	(Domenici et al., 2010)	BC	26.21	0.246	-5.21	0.810	15.07	0.043	25.50	0.017	-14.11	0.097
Thrombopoietin (TPO)		BC	5.30	0.676	15.30	0.673	19.77	0.009	14.39	0.048	---	---
Cortisol	(Chan et al., 2015a; Cubala and Landowski, 2014; Karlovic et al., 2012; Maes et al., 1997; Owens et al., 2014; Papakostas et al., 2013; Rhebergen et al., 2015; Simic et al., 2013; Stetler and Miller, 2011; Wong et al., 2000)	ES,HPA	9.06	0.168	3.23	0.555	6.72	0.002	3.08	0.459	-2.70	0.478
Vascular Endothelial Growth Factor (VEGF)	(Arnold et al., 2012; Bot et al., 2015)	GFS,AG	9.82	0.248	1.16	0.906	9.31	0.035	0.77	0.877	-0.67	0.872
Tenascin-C (TN-C)	(Bot et al., 2015; Stelzhammer et al., 2014)	GFS	-2.30	0.754	6.96	0.566	11.35	0.002	3.63	0.294	-8.48	0.128
Stem Cell Factor (SCF)		GFS	6.07	0.572	-3.33	0.855	12.94	0.004	1.26	0.905	6.90	0.372
Haptoglobin	(Karaoulanis et al., 2014)	IIR	8.19	0.193	5.47	0.461	7.26	0.005	1.99	0.472	0.98	0.711
Interleukin-1 receptor antagonist (IL-1ra)	(Bot et al., 2015; Chan et al., 2015a; Kaestner et al., 2005; Lehto et al., 2010; Stelzhammer et al., 2014)	IIR	-1.31	0.809	18.05	0.084	8.48	0.036	3.68	0.196	0.61	0.921
FASLG Receptor (FAS)		IIR	13.09	0.339	-17.45	0.084	12.21	0.033	-6.27	0.305	6.90	0.073
Carcinoembryonic Antigen (CEA)	(Bot et al., 2015)	O	-5.41	0.336	-13.81	0.153	3.09	0.036	0.06	0.972	1.43	0.573
Prostatic Acid Phosphatase (PAP)		O	-19.35	0.051	-4.98	0.662	9.43	0.025	3.51	0.588	---	---
Cystatin-C	(Bot et al., 2015)	O	18.80	0.223	6.13	0.760	24.14	0.033	---	---	-9.25	0.344
Progesterone	(Abou-Saleh et al., 1998)	ES	-9.99	0.365	-2.26	0.870	4.16	0.130	-13.17	1.84E-04	3.44	0.462

Betacellulin (BTC)	(Lu et al., 2013)	**GFS**	---	---	---	---	**-0.84**	**0.877**	**-15.91**	**0.009**	---	---
Insulin-like Growth Factor I (IGF-I)	(Deuschle et al., 1997; Weber-Hamann et al., 2009)	**GFS,BC**	---	---	---	---	**-3.05**	**0.160**	**-2.39**	**0.040**	---	---
Interleukin-4 (IL-4)	(Domenici et al., 2010; Simon et al., 2008)	**IIR**	---	---	---	---	---	---	**-13.31**	**0.046**	---	---
Eotaxin-3		**IIR**	---	---	---	---	---	---	**-7.34**	**0.009**	---	---
Interleukin-13 (IL-13)	(Chan et al., 2015a; Simon et al., 2008)	**IIR**	**-4.14**	**0.487**	**11.92**	**0.289**	**1.51**	**0.792**	**-6.33**	**0.019**	---	---
Alpha-Fetoprotein (AFP)		**O**	**3.28**	**0.482**	**-6.67**	**0.322**	**1.63**	**0.376**	**-7.47**	**0.034**	---	---
Angiotensin-Converting Enzyme (ACE)	(Chan et al., 2015a; Kaestner et al., 2005; Stelzhammer et al., 2014)	**VR**	**-0.09**	**0.992**	**12.68**	**0.189**	**-7.97**	**0.228**	**-9.36**	**0.015**	**-0.47**	**0.932**
Thrombospondin-1 (TSP-1)		**BC**	**-40.25**	**0.095**	**54.70**	**0.073**	**2.41**	**0.466**	**23.49**	**0.005**	**-0.73**	**0.864**
Insulin	(Arnold et al., 2012; Chan et al., 2015a; Domenici et al., 2010; Okamura et al., 2000)	**CM**	**-4.63**	**0.366**	**-0.74**	**0.939**	**1.28**	**0.626**	**3.42**	**0.008**	**1.99**	**0.314**
Thyroxine-Binding Globulin (TBG)	(Chan et al., 2015a)	**ES,TS**	**-1.52**	**0.948**	**-3.39**	**0.886**	**-10.18**	**0.084**	**16.46**	**0.019**	**-5.68**	**0.411**
C-Reactive Protein (CRP)	(Domenici et al., 2010)	**IIR**	**3.29**	**0.113**	**1.73**	**0.478**	**1.63**	**0.118**	**2.97**	**0.023**	**-1.65**	**0.211**
EN-RAGE	(Bot et al., 2015; Chan et al., 2015a; Kaestner et al., 2005; Stelzhammer et al., 2014)	**IIR**	**-2.09**	**0.543**	**2.11**	**0.734**	**1.08**	**0.620**	**7.61**	**0.005**	**-0.25**	**0.909**
Myeloperoxidase (MPO)	(Papakostas et al., 2013)	**IIR**	**-1.01**	**0.788**	**15.17**	**0.105**	**2.09**	**0.521**	**10.99**	**0.011**	**0.66**	**0.764**
Serum Amyloid P-Component (SAP)	(Domenici et al., 2010)	**IIR**	**3.52**	**0.631**	**0.71**	**0.967**	**-1.26**	**0.849**	**13.22**	**0.005**	**1.59**	**0.777**
Apolipoprotein(a) (Lp(a))	(Domenici et al., 2010)	**LM**	**2.14**	**0.402**	**5.43**	**0.226**	**1.26**	**0.339**	**2.65**	**0.049**	**-0.01**	**0.995**
Matrix Metalloproteinase-10 (MMP-10)	(Bot et al., 2015)	**O**	**-19.53**	**0.050**	**-4.88**	**0.747**	**3.74**	**0.253**	---	---	**10.35**	**0.013**
Collagen IV		**O**	**-0.52**	**0.947**	**9.62**	**0.314**	---	---	---	---	**-7.87**	**0.023**
Glucose-6-phosphate Isomerase (G6PI)		**CM,AG**	---	---	---	---	---	---	---	---	**-8.55**	**0.039**
Insulin-like Growth Factor-Binding Protein 1 (IGFBP-1)		**GFS**	**-2.03**	**0.546**	**1.92**	**0.769**	---	---	---	---	**-3.29**	**0.018**
Beta-2-Microglobulin (B2M)	(Domenici et al., 2010)	**IIR**	**22.90**	**0.079**	**0.70**	**0.967**	**6.94**	**0.344**	**17.18**	**0.107**	**-14.41**	**0.014**
Immunoglobulin A (IgA)	(Gold et al., 2012)	**IIR**	**-5.44**	**0.401**	**2.77**	**0.724**	**5.18**	**0.295**	**0.03**	**0.994**	**-7.41**	**0.039**
Immunoglobulin M (IgM)	(Domenici et al., 2010)	**IIR**	**-7.53**	**0.172**	**-2.26**	**0.743**	**-2.83**	**0.210**	**4.23**	**0.218**	**-9.80**	**0.003**
Monocyte Chemotactic Protein 1 (MCP-1)	(Bai et al., 2014; Chan et al., 2015a; Simon et al., 2008)	**IIR,AG**	**-3.19**	**0.730**	**12.05**	**0.471**	**3.45**	**0.513**	**6.58**	**0.237**	**-12.92**	**0.003**
Platelet-Derived Growth Factor BB (PDGF-BB)		**GFS,AG**	**6.79**	**0.466**	**33.70**	**0.056**	**5.67**	**0.254**	**-4.41**	**0.618**	**-8.84**	**0.029**
Prolactin (PRL)		**ES**	**11.73**	**0.126**	**15.11**	**0.050**	**1.81**	**0.443**	**-3.05**	**0.086**	**-7.95**	**0.020**

β, Regression Coefficient Estimates; **P,** P-value; **Lit Ref,** Literature References; **ADs,** Antidepressants; **Func,** Biological Function; **AG,** Angiogenesis; **AR,** Appetite Regulation; **BC,** Blood Coagulation; **CM,** Carbohydrate Metabolism; **CA,** Cell Adhesion; **ES,** Endocrine Signalling; **GFS,** Growth Factor Signalling; **HPA,** Hypothalamic–Pituitary–Adrenal Axis Signalling; **IIR,** Immune/Inflammatory Response; **IH,** Ion Homeostasis; **LM,** Lipid Metabolism; **O,** Other; **TS,** Thyroid Signalling; **VR,** Vascular Regulation. ***,** LC-MS data as

this protein was not measured by the RBM platform in cohort 4. See Supplementary Table 1 for the full list of proteins measured across each cohort.

Figure legends

Figure 1. Polar histogram showing the biomarkers of treatment response identified across the five independent cohorts.

Key: Direction of association = direction of regression coefficient estimates, which can be positive (β) or negative (-β); **Positive (β)** = higher baseline protein level is associated with better response to treatment; **Negative (-β) =** lower baseline protein level is associated with better response to treatment; **Not significant** = $P<0.05$; **Not measured =** not measured by DiscMAP version used to profile samples in the respective cohort.

Supplementary Figure 1. Association between treatment response and baseline APOA-IV levels in cohorts 1, 3, 4 and 5.