Supplementary Materials

Supplementary Table. Studies Examining the Impact of Antidepressant Treatment on the Inflammatory Response

Author	Population	Treatment	Treatment Duration	Immune Biomarker	Result
Maes *et al.* 1995 (118)	Inpatient Major Depression (n=17)	Fluoxetine (n=9) TCA (n=8)	Mean ~12 weeks	Plasma IL-6, sIL-6R, sIL-2R, TfR	Antidepressant treatment had no effect on immune biomarkers.
Sluzewska *et. al.* 1995 (119)	Inpatient Major Depression (n=22)	Fluoxetine	8 weeks	Serum IL-6, AGP and CRP	IL-6 decreased in those with elevated IL-6 concentrations at baseline. AGP concentrations also decreased.
Maes *et al.* 1997 (120)	Major Depression (n=25)	Trazodone alone or in combination with Pindolol or Fluoxetine	5 weeks	Serum IL-6, sIL-6R, IL-1ra, CC16, sCD8	sIL-6R significantly decreased with antidepressant treatment. No differences between responders and non-responders were found.
Sluzewska *et. al.* 1997 (108)	Refractory Depression (n=32), Controls (n=20)	Lithium potentiation of antidepressant therapy	4 weeks	Plasma APPs including CRP	APP decreased in lithium-treated subjects. Baseline APPs were increased in non-responders.
Hinze-Seich *et al.* 2000 (121)	Inpatient Major Depression (n=22) and Inpatient Other Diagnoses (n=14)	TCA (n=12), paroxetine (n=10), no medication (n=14)	6 weeks	Plasma TNF-alpha and TNF soluble receptors	sTNFR2 increased with TCA therapy, and was associated with increased BMI. There was no change in TNF-alpha.
Kubera *et al.* 2000 (122)	Major depression (n=9), Controls (n=11)	Antidepressants (not specified)	6 weeks	Serum IL-6, IL-1ra and IL-10	Antidepressant treatment had no effect on serum cytokines.
Lanquillon *et al.* 2000 (107)	Inpatient Major Depression (n=24)	Amitriptyline	6 weeks	Unstimulated blood production of IL-6 and TNF-alpha, CRP	TNF-alpha decreased in responders. Non-responders exhibited increased baseline IL-6. Baseline CRP was elevated in major depression patients versus controls.
Kagaya *et al.* 2001(123)	Major Depression and Dysthymia (n=12), Controls (n=12)	Multiple Antidepressants	4 weeks	Plasma IL-1 beta, IL-6, sIL-2R, TNF-alpha	TNF-alpha increased following treatment in 8 patients.
Kraus *et al.* 2002 (124)	Major Depression (n=20)	Mirtazapine (n=11), Venlafaxine (n=9)	4 weeks	Plasma TNF-alpha and TNF soluble receptors	TNF-alpha and its soluble receptors increased with mirtazapine in association with increased BMI. Venlafaxine had no effect on immune measures.
Tuglu *et al.* 2003 (125)	Inpatient Major Depression (n=26), Controls (n=17)	Multiple SSRIs	6 weeks	Serum TNF-alpha and CRP	TNF-alpha decreased during treatment to levels comparable to controls. CRP decreased in antidepressant treated subjects.
Basterzi *et al.* 2005 (126)	Major Depression (n=23), Controls (n=23)	Multiple SSRIs	6 weeks	Serum IL-6	Antidepressants reduced IL-6 in patients below baseline levels of patients and controls. Baseline IL-6 levels were somewhat higher in patients versus controls but not significantly.
O'Brien *et al.* 2006 (127)	Major Depression with melancholic features (n=20, all women)	Multiple SSRIs	3 weeks	Serum CRP	CRP concentrations decreased following antidepressant treatment irrespective of response.
Narita *et al.* 2006 (128)	Remitted Depression (n=21), Controls (n=20)	Multiple SSRIs or SNRI	Maintenance (mean ~18 months)	Plasma TNF-alpha	TNF-alpha was lower in patients versus controls.
Himmerich *et al.* 2006 (129)	Affective Spectrum Disorder (n=70)	Multiple medications prior to and during admission	Mean ~11 weeks	Plasma TNF-alpha and TNF soluble receptors	TNF-alpha soluble receptors increased during hospitalization. No change in TNF-alpha. Patients exhibited reduced depressive symptoms upon discharge compared to admission.
Marques-Deak *et al.* 2007 (130)	Major Depression (n=27, all women)	Imipramine (n=12) or sertraline (n=15)	3 months to 1 year	LPS-stimulated IL-1 beta, IL-6 and IFN-gamma	All cytokines increased after treatment.
Kim *et al.* 2007 (131)	Inpatient Major Depression (n=32)	Multiple antidepressants	6 weeks	LPS- and PHA-stimulated IL-6, TNF-alpha, IFN-gamma, IL-2, IL-4, TGF-beta	IL-6, IL-2 and TGF-beta were decreased following treatment.
Eller *et al.* 2007 (132)	Major Depression (n=100), Controls (n=45)	Escitalopram	12 weeks	Serum TNF-alpha, sIL-2R, IL-8	sIL-2R decreased with treatment. TNF-alpha was higher in non-responders.
Sutcigil *et al.* 2007 (133)	Major Depression (n=23), Controls (n=25)	Sertraline	8 weeks	Serum IL-2, IL-4, IL-12, MCP-1, TGF-beta, TNF-alpha,	IL-2, IL-12, MCP-1 and TNF-alpha were higher and IL-4 and TGF-beta were lower in patients versus controls at baseline. IL-2, IL-12, MCP-1, and TNF-alpha decreased and IL-4 and TGF-beta increased after treatment.

Hernandez *et al.* 2008 (134)	Major Depression (n=31), Controls (n=22)	Multiple SSRIs	52 weeks	Serum IL-1 beta, IL-2, IL-4, IL-10, IL-13, IFN-gamma	IL-10 and IL-13 were higher and IL-2, IL-1 beta, and IFN-gamma were lower in depressive versus controls. IL-1 beta, IL-2, IL-4, and IFN-gamma increased and IL-10 and IL-13 decreased after 52 weeks of treatment (n=10 at the end of the study).
Eller *et al.* 2008 (135)	Major Depression (n=28 non-responders to escitalopram) Controls (n=45)	Escitalopram plus Bupropion	6 weeks	Serum TNF-alpha, sIL-2R, IL-8	IL-8 increased during adjunctive bupropion treatment in responders and non-responders.

AGP: alpha 1 acid glycoprotein; APP: acute phase proteins; BMI: body mass index; CC16: Clara cell protein; CRP: C-reactive protein; IFN: interferon; IL: interleukin; IL-1ra: IL-1 receptor antagonist; LPS: lipopolysaccharide; MCP-1: monocyte chemoattractant protein-1; PHA: phytohemaglutinin; sCD8: soluble cluster of differentiation 8; sIL-2R: soluble IL-2 receptor; sIL-6R: soluble IL-6 receptor; SNRI: serotonin norepinephrine re-uptake inhibitor; SSRI: selective serotonin reuptake inhibitor; sTNFR2: soluble TNF-alpha receptor 2; TCA: tricyclic antidepressant; TGF: transforming growth factor; TfR: transferrin receptor; TNF: tumor necrosis factor

Supplementary References

107. Lanquillon S, Krieg JC, Bening-Abu-Shach U, Vedder H (2000): Cytokine production and treatment response in major depressive disorder. *Neuropsychopharmacol* 22: 370-379.

108. Sluzewska A, Sobieska M, Rybakowski JK (1997): Changes in acute-phase proteins during lithium potentiation of antidepressants in refractory depression. *Neuropsychobiol* 35: 123-127.

118. Maes M, Meltzer HY, Bosmans E, Bergmans R, Vandoolaeghe E, Ranjan R, *et al.* (1995): Increased plasma concentrations of interleukin-6, soluble interleukin-6, soluble interleukin-2 and transferrin receptor in major depression. *J Affect Disord* 34: 301-309.

119. Sluzewska A, Rybakowski J, Laciak M, Mackiewicz A, Sobieska M, Wiktorowicz K (1995): Interleukin-6 serum levels in depressed patients before and after treatment with fluoxetine. *Ann NY Acad Sci* 762: 474-476.

120. Maes M, Westenberg H, Vandoolaeghe E, Demedts P, Wauters A, Neels H, *et al.* (1997): Effects of trazodone and fluoxetine in the treatment of major depression: therapeutic pharmacokinetic and pharmacodynamic interactions through formation of meta-chlorophenylpiperazine. *J Clin Psychopharmacol* 17: 358-364.

121. Hinze-Selch D, Schuld A, Kraus T, Kuhn M, Uhr M, Haack M, *et al.* (2000): Effects of antidepressants on weight and on the plasma levels of leptin, TNF-alpha and soluble TNF receptors: A longitudinal study in patients treated with amitriptyline or paroxetine. *Neuropsychopharmacol* 23: 13-19.

122. Kubera M, Kenis G, Bosmans E, Zieba A, Dudek D, Nowak G, *et al.* (2000): Plasma levels of interleukin-6, interleukin-10, and interleukin-1 receptor antagonist in depression: comparison between the acute state and after remission. *Pol J Pharmacol* 52: 237-241.

123. Kagaya A, Kugaya A, Takebayashi M, Fukue-Saeki M, Saeki T, Yamawaki S, *et al.* (2001): Plasma concentrations of interleukin-1beta, interleukin-6, soluble interleukin-2 receptor and tumor necrosis factor alpha of depressed patients in Japan. *Neuropsychobiol* 43: 59-62.

124. Kraus T, Haack M, Schuld A, Hinze-Selch D, Koethe D, Pollmacher T (2002): Body weight, the tumor necrosis factor system, and leptin production during treatment with mirtazapine or venlafaxine. *Pharmacopsychiatry* 35: 220-225.

125. Tuglu C, Kara SH, Caliyurt O, Vardar E, Abay E (2003): Increased serum tumor necrosis factor-alpha levels and treatment response in major depressive disorder. *Psychopharmacol (Berl)* 170: 429-433.

126. Basterzi AD, Aydemir C, Kisa C, Aksaray S, Tuzer V, Yazici K, *et al.* (2005): IL-6 levels decrease with SSRI treatment in patients with major depression. *Hum Psychopharmacol* 20: 473-476.

127. O'Brien SM, Scott LV, Dinan TG (2006): Antidepressant therapy and C-reactive protein levels. *Br J Psychiatry* 188: 449-452.

128. Narita K, Murata T, Takahashi T, Kosaka H, Omata N, Wada Y (2006): Plasma levels of adiponectin and tumor necrosis factor-alpha in patients with remitted major depression receiving long-term maintenance antidepressant therapy. *Progr Neuropsychopharmacol Biol Psychiatry* 30: 1159-1162.

129. Himmerich H, Binder EB, Kunzel HE, Schuld A, Lucae S, Uhr M, *et al.* (2006): Successful antidepressant therapy restores the disturbed interplay between TNF-alpha system and HPA axis. *Biol Psychiatry* 60: 882-888.

130. Marques-Deak AH, Neto FL, Dominguez WV, Solis AC, Kurcgant D, Sato F, *et al.* (2007): Cytokine profiles in women with different subtypes of major depressive disorder. *J Psychiatr Res* 41: 152-159.

131. Kim YK, Na KS, Shin KH, Jung HY, Choi SH, Kim JB (2007): Cytokine imbalance in the pathophysiology of major depressive disorder. *Prog Neuropsychopharmacol Biol Psychiatry* 31: 1044-1053.

132. Eller T, Vasar V, Shlik J, Maron E (2008): Pro-inflammatory cytokines and treatment response to escitalopram in major depressive disorder. *Prog Neuropsychopharmacol Biol Psychiatry* 32: 445-450.

133. Sutcigil L, Oktenli C, Musabak U, Bozkurt A, Cansever A, Uzun O, *et al.* (2007): Pro- and anti-inflammatory cytokine balance in major depression: effect of sertraline therapy. *Clin Dev Immunol* 2007: 76396.

134. Hernandez ME, Mendieta D, Martinez-Fong D, Loria F, Moreno J, Estrada I, *et al.* (2008): Variations in circulating cytokine levels during 52 week course of treatment with SSRI for major depressive disorder. *Eur Neuropsychopharmacol* 18(12):917-24.

135. Eller T, Vasar V, Shlik J, Maron E (2008): Effects of bupropion augmentation on pro-inflammatory cytokines in escitalopram-resistant patients with major depressive disorder. *J Psychopharmacol* [published online ahead of print Jun 18].