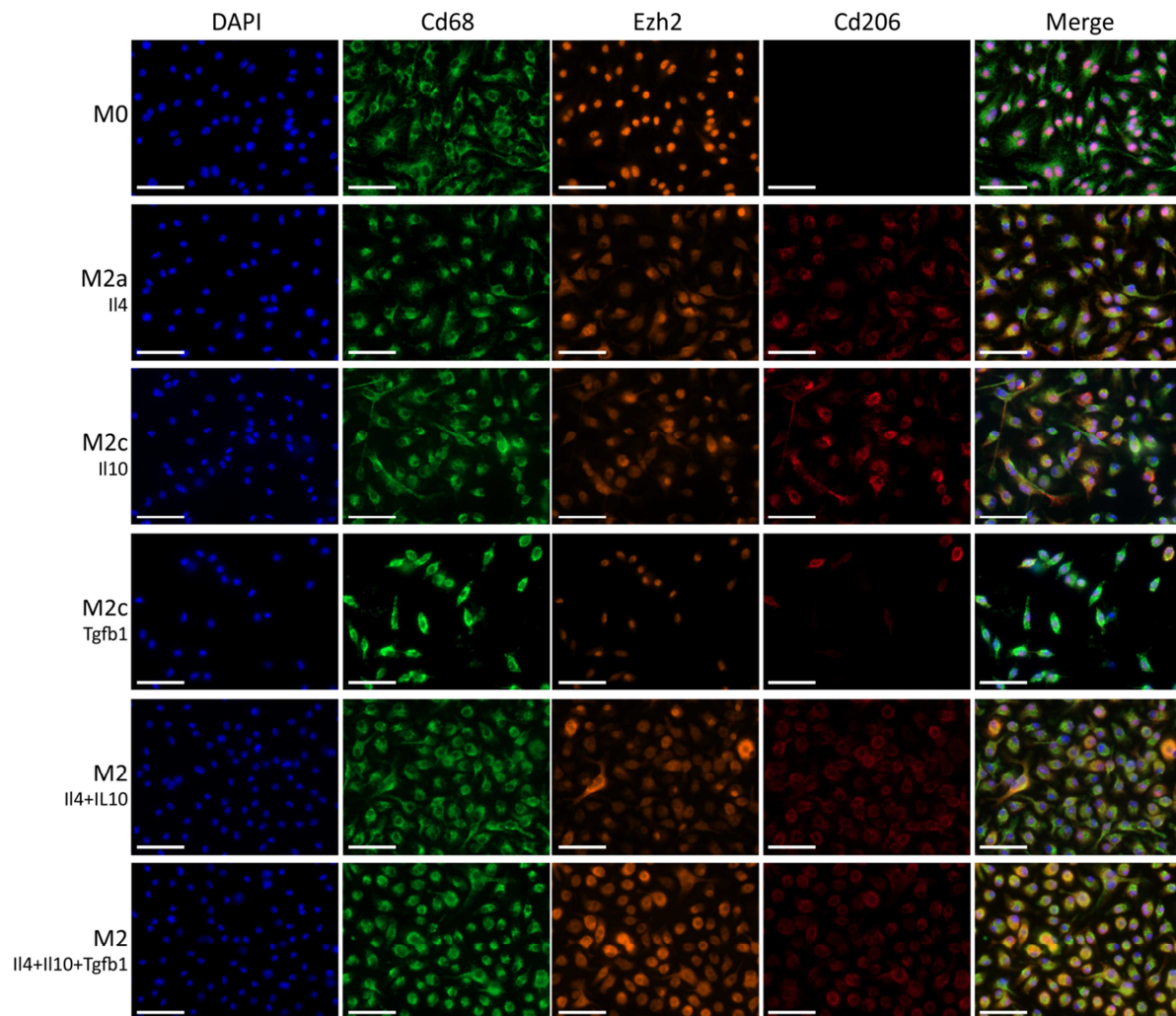


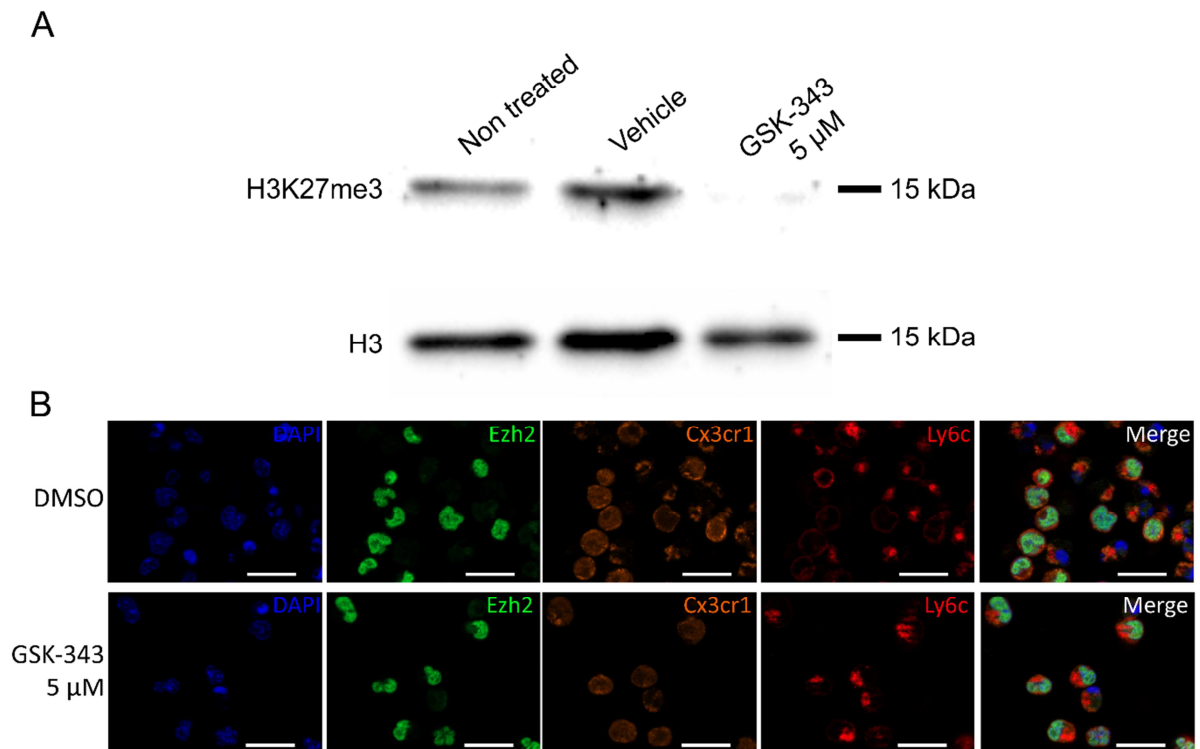
Supplementary information



Supplementary figure S1: Ezh2 cytoplasmic translocation is not restricted to a single M2 macrophage phenotype

Representative pictures of immunostaining for mature non-polarized M0 macrophages, M2 differentially polarized macrophages with either single IL4 for M2a, IL10 or Tgfb1 for M2c, or combinations of cytokines *in vitro*. Nuclei were stained with DAPI (blue), macrophages with Cd68 (*green*) and M2 polarization was assessed based on Cd206 (*red*) expression. Ezh2 (orange) cellular localization was observed in all cell type but only appeared in M2 macrophages cytoplasm. Scale bars represent 50 μm .

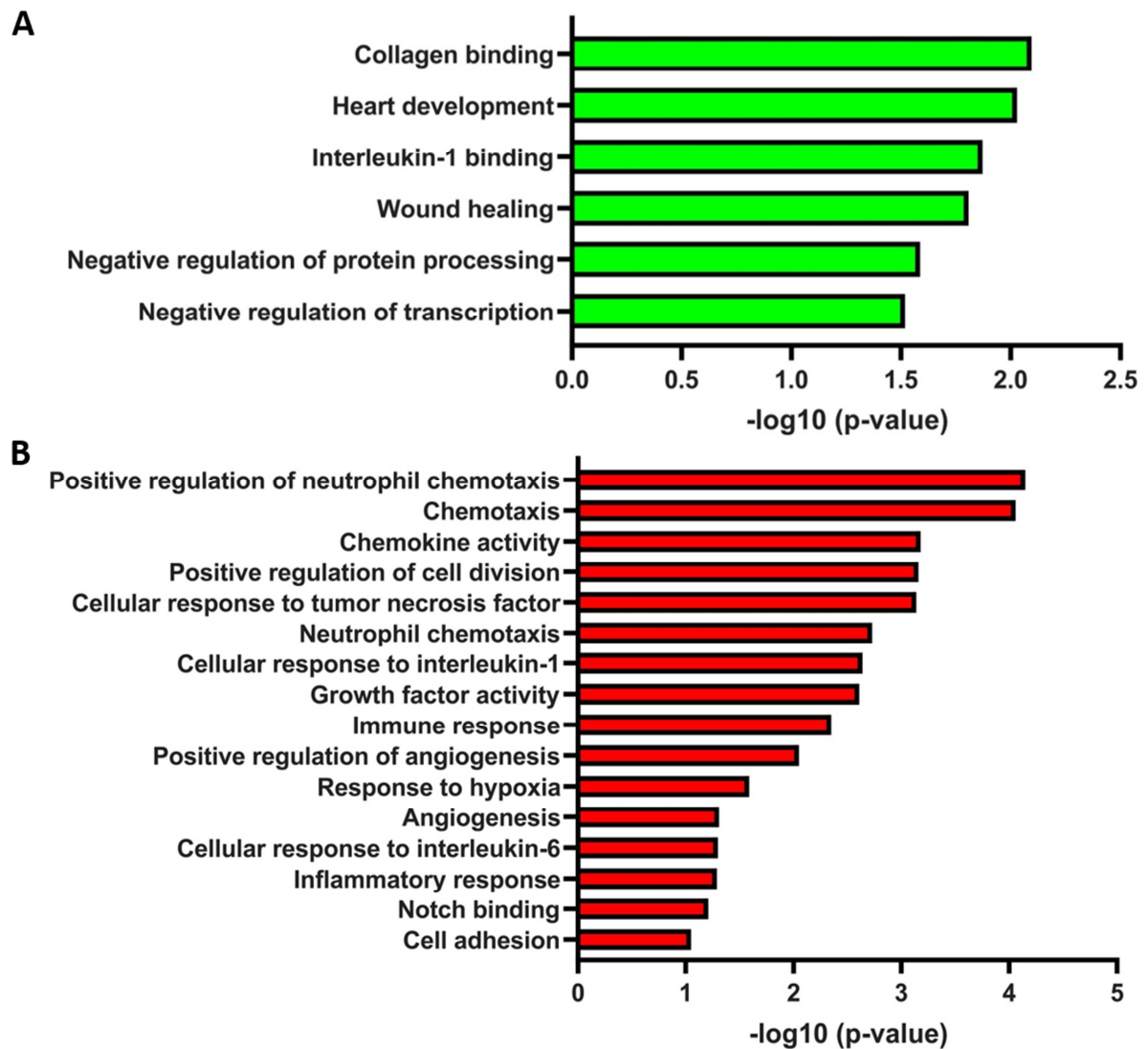
**Supplementary table 1: list of bivalent genes identified by ChIP-Sequencing in
CD14+human monocytes**



Supplementary figure S2: GSK-343 reduces H3K27me3 levels without altering Ezh2 expression in murine monocytes

((A) GSK-343-treatment in murine monocytes (TIB-204 cell line) decreased histone H3K27me3 levels, as determined by western blot. Molecular weights are indicated in kDa. Total histone H3 serves as loading control.

(B) Representative pictures of immunostaining of mouse monocytes treated for 72h with vehicle or GSK-343 (5 μ M). Nuclei were stained with DAPI (*blue*), Ezh2 (*green*) cellular localization was analyzed in Cx3cr1 (*orange*) and Ly6c (*red*) expressing monocytes. Scale bars represent 25 μ m.



Supplementary figure S3: GSK-343 treatment of human monocytes promotes expression of genes regulating chemotaxis and angiogenesis

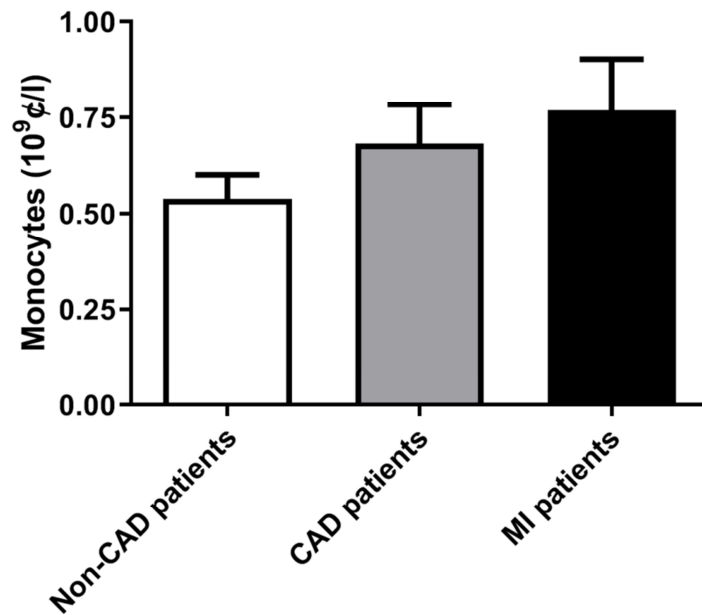
Representative Gene Ontology (GO) Biological Process categories significantly enriched for down- (A) and up-regulated (B) genes in human monocytes treated with GSK-343 as determined by mRNA-Seq.

**Supplementary table 2: list of down-regulated genes and related GO categories
in human monocytes treated with GSK-343**

Supplementary table 3: list of up-regulated genes and related GO categories in selected circulating human monocytes treated with GSK-343

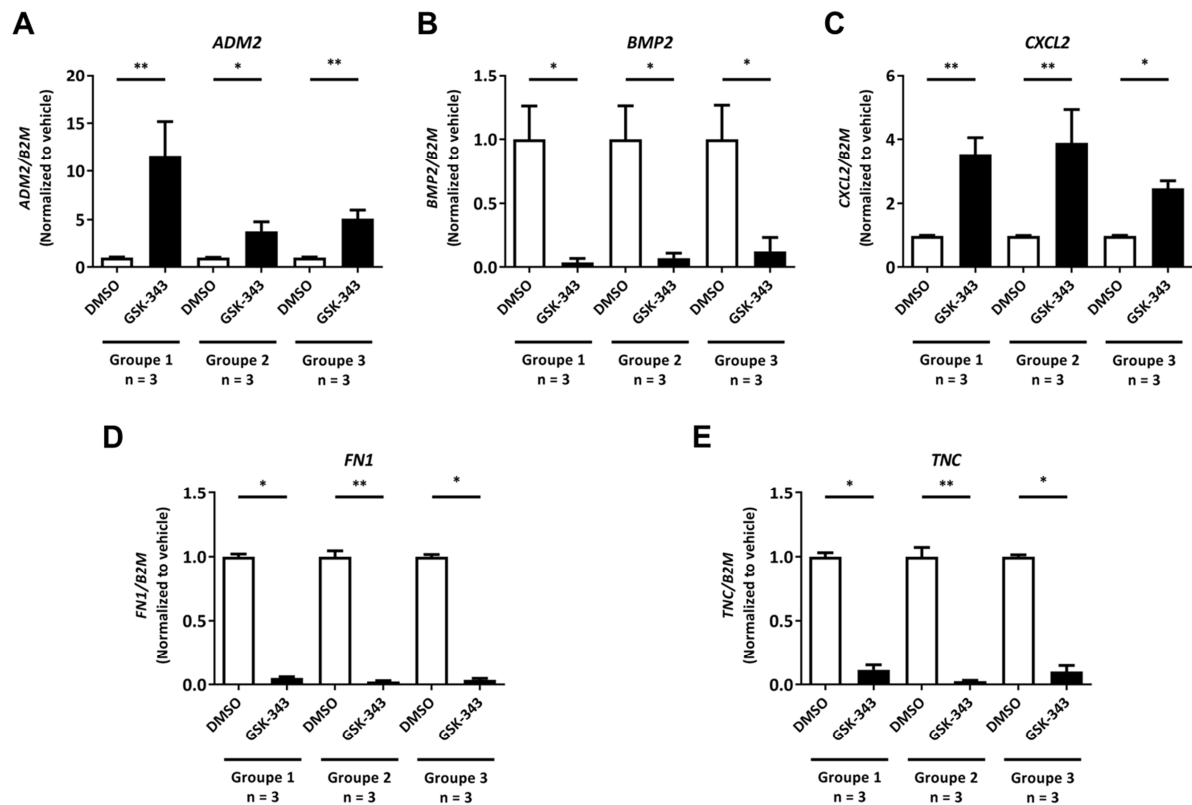
	Group 1	Group 2	Group 3	Overall
	Non-CAD	CAD	AMI	n = 48
	n = 20	n = 21	n = 7	
Age (year)	71±10	77±10	67±10	73±10
Gender (M/F)	10/10	16/5	5/2	21/17
Erythrocytes (10 ¹² ¢/l)	4.46±0.50	4.50±0.54	5.31±0.61	4.59±0.61
Leucocytes (10 ⁹ ¢/l)	6.68±1.82	7.75±1.79	13.22±6.26	8.10±3.54
Granulocyte Neutrophils (10 ⁹ ¢/l)	4.22±1.56	5.29±1.52	10.08±6.03	5.55±3.26
Granulocyte Eosinophils (10 ⁹ ¢/l)	0.19±0.15	0.20±0.13	0.07±0.06	0.18±0.14
Granulocyte Basophils (10 ⁸ ¢/l)	0.45±0.24	0.51±0.31	0.46±0.39	0.47±0.29
Lymphocytes (10 ⁹ ¢/l)	1.59±0.70	1.62±0.57	2.27±1.66	1.70±0.86
Monocytes (10 ⁹ ¢/l)	0.63±0.18	0.69±0.25	0.76±0.30	0.68±0.23
Platelets (10 ⁹ ¢/l)	234.9±58.9	227.4±51.2	279.0±94.1	238.1±63.0

Supplementary table 4: patient characteristics



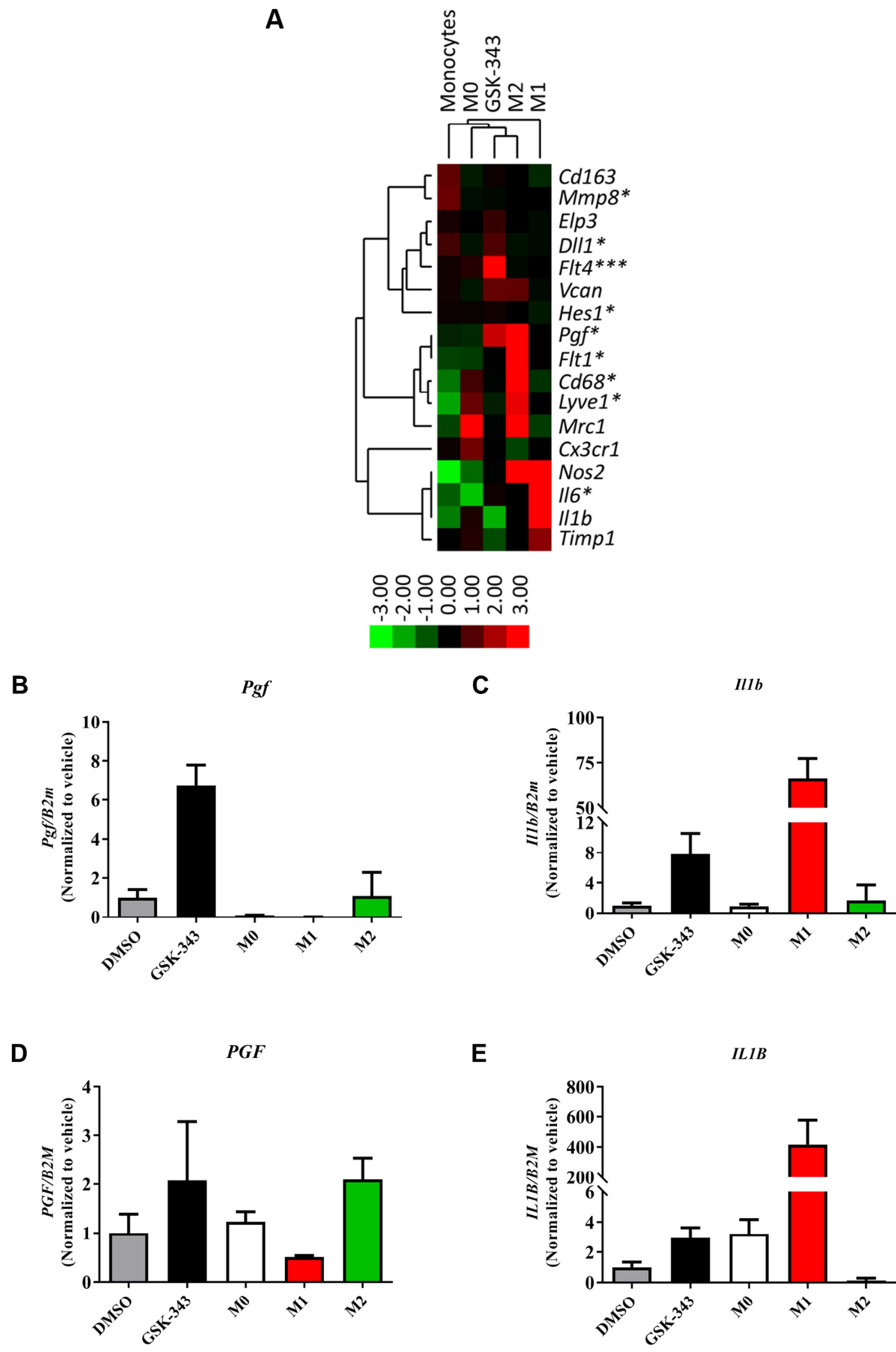
Supplementary figure S4: Levels of selected circulating monocytes in MI patients as compared to non-CAD and CAD patients

Blood-derived human monocyte quantification, obtained after negative magnetic selection. Data is represented as mean number of live selected monocytes obtained per ml of collected blood, Non-CAD (n=20), CAD (n=21) and MI (n=7) patients $\pm$ SEM.



Supplementary figure S5: Reduced and enhanced expression of genes identified by RNA-seq upon GSK-343 treatment

Expression of ADM2 (A), BMP2 (B), CXCL2 (C), FN1 (D) and TNC (E) in treated human monocytes from different patient groups with vehicle or GSK-343 was measured par RT-qPCR. Data are presented as mean expression to fold of vehicle treated monocytes $\pm$ SEM. Group 1 Non-CAD (n=3), group 2 CAD (n=3) and group 3 AMI (n=3). The p values are depicted as asterisks in the figures as follows: **p <0.01; *p <0.05.



Supplementary figure S6: EZH2 inhibition with GSK-343 brings monocytes closer to M2 than any other myeloid cell types

Gene expression in monocytes treated with vehicle or GSK-343 or following *in vitro* differentiation of monocytes into M0, M1 or M2 macrophages from TIB-204 monocyte mouse cell line (A) or mouse primary circulating selected monocytes (B and C) or human primary circulating selected monocytes (D and E) was measured by RT-qPCR. Data are presented as a targeted transcriptomic array of selected genes for each cell type categories derived from TIB-204 (A) or mean expression reported vehicle treated monocytes $\pm$ SEM for mouse primary circulating selected monocytes (B and C) or human primary circulating selected monocytes (D and E). The p values are depicted as asterisks in the figures as follows: ***p <0.001; **p <0.01; *p <0.05; ns: non-significant.

	3 days post-MI			8 days post MI		
	Sham (n=4)	vehicle (n=7)	GSK-343 (n=5)	Sham (n=4)	vehicle (n=5)	GSK-343 (n=8)
Cardiomyocyte sizes (μm^2)	ND	450.86 $\pm$ 28.9 ns	492.50 $\pm$ 12.8 ns	398.5 $\pm$ 19.5	546.80 $\pm$ 43.80 *	441.87 $\pm$ 23.6 #
Capillary density (Blood vessels/mm²)	ND	1681.28 $\pm$ 179.3 ***	1783.40 $\pm$ 228.6 ns	2439.5 $\pm$ 179.6	1521.0 $\pm$ 189.0 ***	1774.25 $\pm$ 199.85 ns
Open lymphatic vessel density (vessels/mm²)	ND	7.17 $\pm$ 2.09 ns	5.87 $\pm$ 2.02 ns	5.47 $\pm$ 1.25	10.34 $\pm$ 2.33 p=0.07	6.68 $\pm$ 1.97 ns
Total macrophages (cells/field)	ND	30.58 $\pm$ 1.88 *	38.22 $\pm$ 3.26 p=0.11	23.48 $\pm$ 1.77	38.98 $\pm$ 4.16 ***	39.76 $\pm$ 5.05 ns

Supplementary table 5: Histologic cardiac parameters

Quantitative analysis of histologic cardiac parameters in border zone (BZ) of sham, vehicle and GSK-343 treated mice at 3- and 8-days post-MI. Data are presented as means $\pm$ SEM. Asterisk (*) and hashtag (#) symbols indicates statistically significant difference compared to sham and vehicle condition respectively after Kruskal-Wallis test. # p <0.05, ns non-significant, * p <0.05*** p <0.001. ND indicates Not Determined values.

Gene function	Gene name	3 days post-MI			8 days post MI		
		sham	vehicle	GSK-343	sham	vehicle	GSK-343
Inflammation	<i>Ccl2</i>	1.00 ± 0.19	4.41 ± 0.47 ***	4.08 ± 0.37 ***	See figure 6b		
	<i>Ccl21</i>	1.00 ± 0.23	0.65 ± 0.04 ns	0.62 ± 0.07 ns	See figure 6b		
	<i>Il1b</i>	1.00 ± 0.19	1.66 ± 0.14 **	1.51 ± 0.10 ns	See figure 6b		
	<i>Il6</i>	1.00 ± 0.28	3.97 ± 0.32 ***	5.31 ± 0.58 ***	See figure 6b		
	<i>Il10</i>	1.00 ± 0.21	1.62 ± 0.14 *	1.67 ± 0.14 *	1.00 ± 0.13	1.09 ± 0.11 ns	0.97 ± 0.10 ns
	<i>Irf4</i>	1.00 ± 0.25	0.46 ± 0.03 ***	0.51 ± 0.04 ***	1.00 ± 0.10	0.58 ± 0.03 ***	0.66 ± 0.04 **
	<i>Tnf</i>	1.00 ± 0.27	1.50 ± 0.10 ns	1.47 ± 0.09 ns	1.00 ± 0.11	1.56 ± 0.12 *	1.52 ± 0.13 ns
Angiogenesis	<i>Dll1</i>	1.00 ± 0.30	0.59 ± 0.03 ns	0.61 ± 0.04 ns	See figure 6b		
	<i>Vegfa</i>	1.00 ± 0.23	0.65 ± 0.04 **	0.74 ± 0.06 ns	1.00 ± 0.08	0.69 ± 0.03 *	0.71 ± 0.05 *
Fibrosis	<i>Fn1</i>	1.00 ± 0.31	5.64 ± 0.65 ***	6.66 ± 0.81 ***	See figure 6b		
	<i>TnC</i>	1.00 ± 0.29	10.63 ± 1.91 ***	10.92 ± 2.15 ***	See figure 6b		
Cardiac dysfunction	<i>Mb</i>	1.00 ± 0.19	0.61 ± 0.03 ns	0.63 ± 0.05 ns	See figure 6b		
	<i>Nppa</i>	1.00 ± 0.29	2.04 ± 0.26 ns	2.01 ± 0.25 ns	1.00 ± 0.30	2.59 ± 0.38 **	2.19 ± 0.29 ns
	<i>Nppb</i>	1.00 ± 0.18	1.77 ± 0.19 ns	2.18 ± 0.27 *	See figure 6b		
	<i>Tnni3</i>	1.00 ± 0.20	0.61 ± 0.03 ***	0.63 ± 0.06 **	See figure 6b		
	<i>Tnnt2</i>	1.00 ± 0.28	0.96 ± 0.06 ns	1.07 ± 0.17 ns	1.00 ± 0.10	0.66 ± 0.03 ns	0.77 ± 0.06 ns

Supplementary table 6: Inflammation, angiogenesis, fibrosis and cardiac dysfunction gene expression

Cardiac transcript levels of indicated genes measured by RT-qPCR from sham (n=8), or vehicle (n=16) or GSK-343-treated (n=18) mice at 3 and 8 days after MI. Values expressed as mean percentages of sham $\pm$ SEM with B2m serving as internal control. Asterisk (*) symbols indicates statistically significant difference compared to sham condition. ns non-significant, * $p < 0.05$, *** $p < 0.001$.

	3 days post-MI			7 days post MI		
	sham	vehicle	GSK-343	sham	vehicle	GSK-343
LV dilatation index	0.190 ± 0.01	0.166 ± 0.06 ns	0.180 ± 0.04 ns	See figure 6e		
LVED (mm)	3.75 ± 0.09	4.27 ± 0.10 *	4.21 ± 0.09 ns	See figure 6f		
LVES (mm)	2.94 ± 0.10	3.66 ± 0.12 **	3.49 ± 0.11 ns	See figure 6g		
LVFS (%)	21.49 ± 1.73	14.50 ± 1.43 *	15.94 ± 1.43 ns	See figure 6h		
LVEF (%)	44.09 ± 3.10	30.19 ± 2.76 *	33.39 ± 2.70 ns	See figure 6i		
Cardiac output (ml/min)	9.45 ± 1.32	9.98 ± 0.94 ns	10.59 ± 0.90 ns	13.33 ± 1.05	11.07 ± 1.31 ns	12.04 ± 1.29 ns
Heart rate (bpm)	378.7 ± 18.57	394.8 ± 11.66 ns	406.0 ± 7.41 ns	410.4 ± 12.34	425.2 ± 14.22 ns	429.6 ± 13.24 ns
LV mass (mg)	72.21 ± 1.61	85.32 ± 5.51 ns	94.65 ± 2.88 ns	74.98 ± 6.51	108.10 ± 5.34 *	100.80 ± 7.38 ns
Stroke volume (μl)	26.54 ± 2.47	24.82 ± 2.36 ns	26.07 ± 2.05 ns	32.18 ± 1.97	26.92 ± 3.18 ns	27.91 ± 2.54 ns

Supplementary table 7: Echocardiographic cardiac dysfunction parameters

Quantitative analysis of echocardiographic cardiac parameters in sham (n=8), vehicle (n=14) and GSK-343 (n=18) treated mice at 3- and 7-days post-MI. Data are presented as means ± SEM. Asterisk (*) symbols indicates statistically significant difference compared to sham condition. ns non-significant, * p <0.05, *** p <0.001.