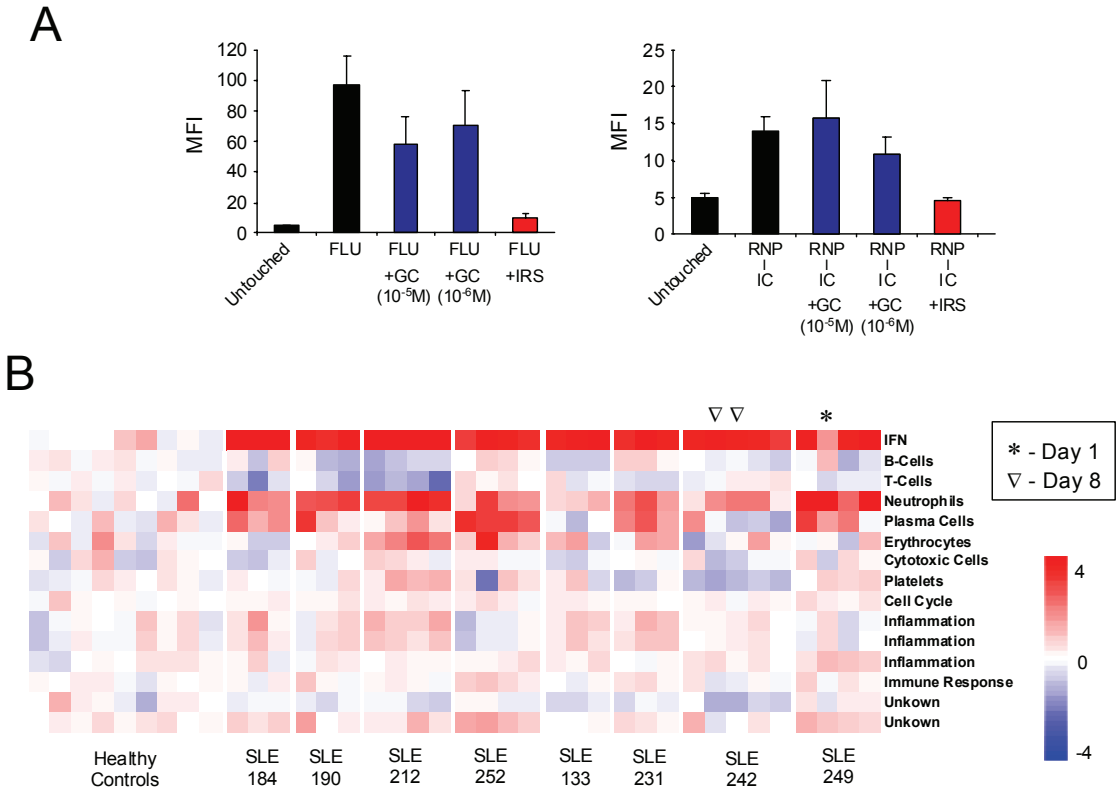
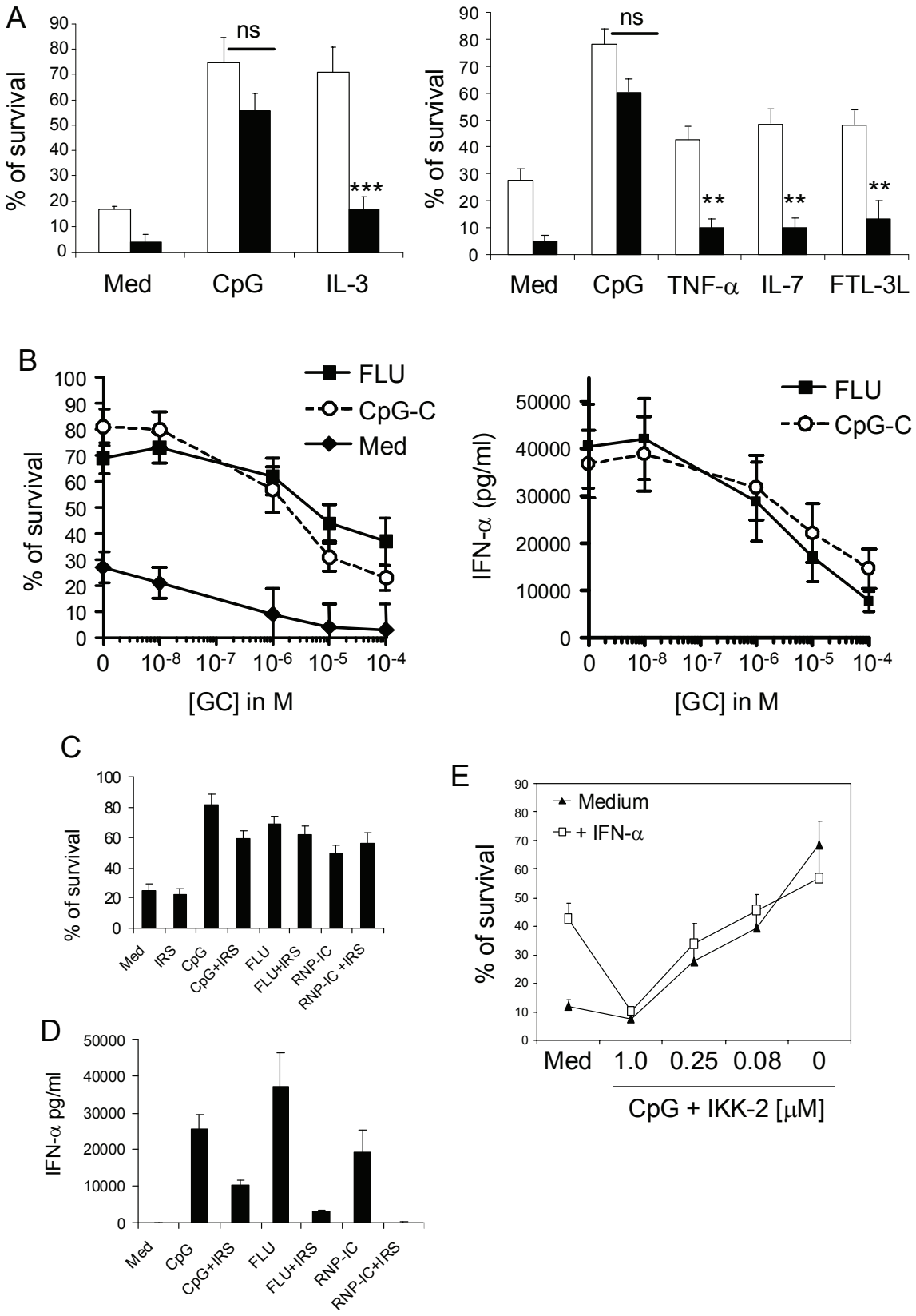
SUPPLEMENTARY INFORMATION



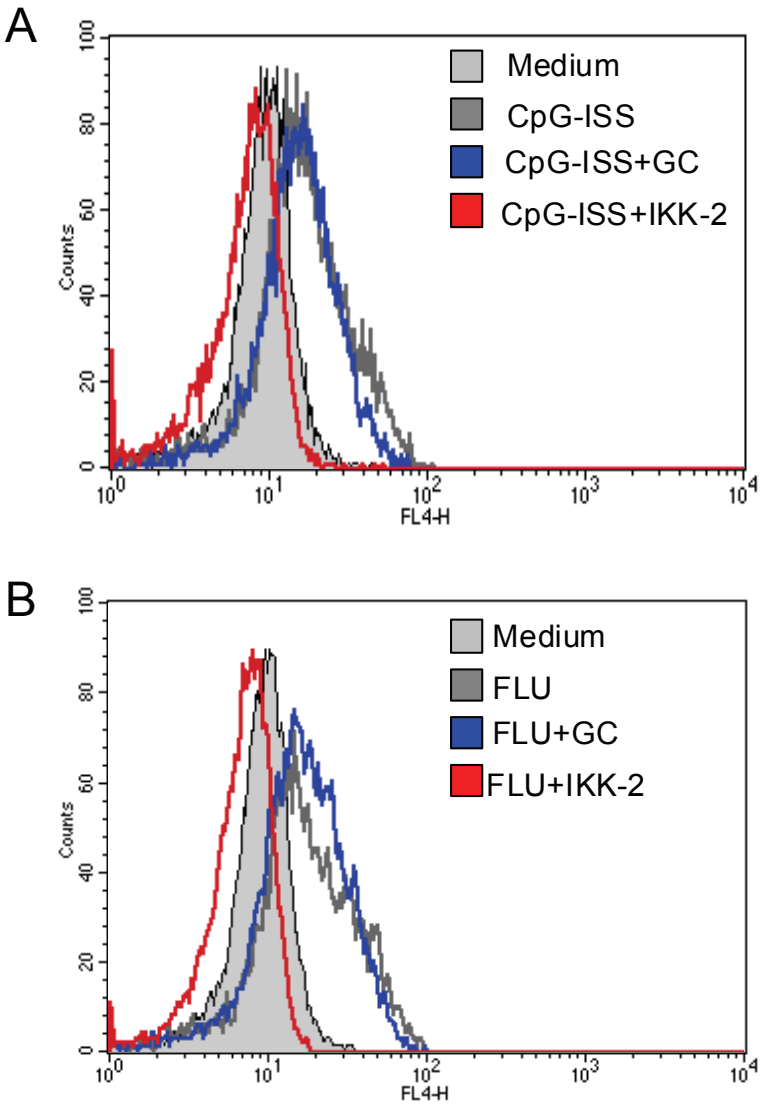
Supplementary Figure 1: Transient levels of the PDC-induced IFN signature in GC-treated SLE patients.

(A) Purified human PDC were cultured alone or in the presence of Flu (2 MOI) or purified anti-RNP IC isolated from SLE patients either alone or combined with GC (10^{-5}M or 10^{-6}M or IRS (0.5 μM). After 3 hr, cells were assayed for IFN-α secretion and cumulative data of five donors shown as MFI (mean ± standard error of the mean). (B) Nanostring nCounter system was used to assess the longitudinal blood gene expression levels in healthy donors and SLE patients. Probes corresponding to 12 IFN-inducible genes were included in Nanostring codeset (see supplemental table 1). Gene expression levels were normalized to control genes and to healthy donors. Heatmap (log 2 scale) corresponding to 8 SLE patient longitudinal samples (individual columns) is shown. Samples corresponding to patients SLE184, 190, 212, 252, 133 and 231 were obtained at 2-3 month intervals. These patients were receiving oral GC but no IV Methylprednisolone pulses. SLE 242 was analyzed the day before an IV pulse, 8 days after 2 independent IV pulses (marked as ∇), and 2 additional times while on oral GC. SLE 249 was analyzed the day before and the day after an IV pulse (marked as *), and two additional times while on oral GC. Only the day after IV pulse there was a decrease in the expression levels of IFN-inducible genes. Red: over expression. Blue: under expression.



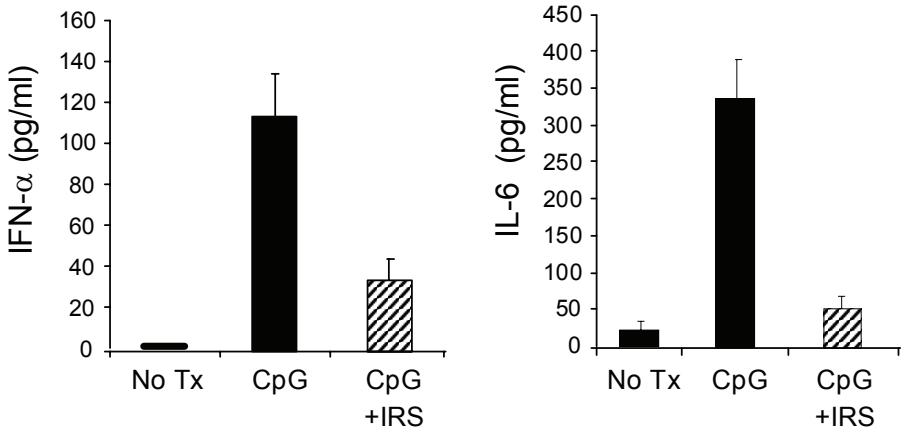
Supplementary Figure 2: TLR-induced signal protect PDC from GC-induced cell death. IRS inhibits IFN-α production in TLR7/9 stimulated human PDC but does not induce cell death and exogenous IFN-α does not rescue PDC in absence of NF-kB activation.

(A) Purified human PDC were cultured with CpG-C ISS (0.5 μM), IL-3 (5 ng/ml), TNF-α (20 ng/ml), IL-7 (10 ng/ml), FTL-3L (10 ng/ml) alone (white bar) or in the presence of GC (10^{-5}M) (black bar). Viability was assessed after 24 hr. Average of 10 (left panel) and 13 (right panel) independent donors ± standard error of the mean in five independent experiments is shown ** $p \leq 0.01$, *** $p \leq 0.001$. P values are between CpG + GC and cytokines + GC groups. (B) Purified human PDC were cultured with CpG-C ISS (0.5 μM), Flu (2 MOI) either alone or in combination with various concentration of GC. Viability and production of IFN-α was assessed after 24 hr. Average of 10 independent donors is shown. (C, D) Purified PDC were cultured with CpG-C ISS (0.5 μM), Flu (2 MOI) or RNP-IC (0.5 mg/ml) either alone or in the presence of IRS (1μM) (C) Viability was assessed after 24 hr. (D) IFN-α was measured by ELISA. Cumulative data of three independent experiments is shown. *n*=10. (E) Purified PDC were cultured with CpG-C ISS (0.5 μM) with or without soluble IFN-α (20 ng/ml) either alone or in the presence of the NF-kB inhibitor IKK-2 at the indicated concentrations. Viability was assessed after 24 hr. Average ± standard error of the mean of 10 independent donors is shown.



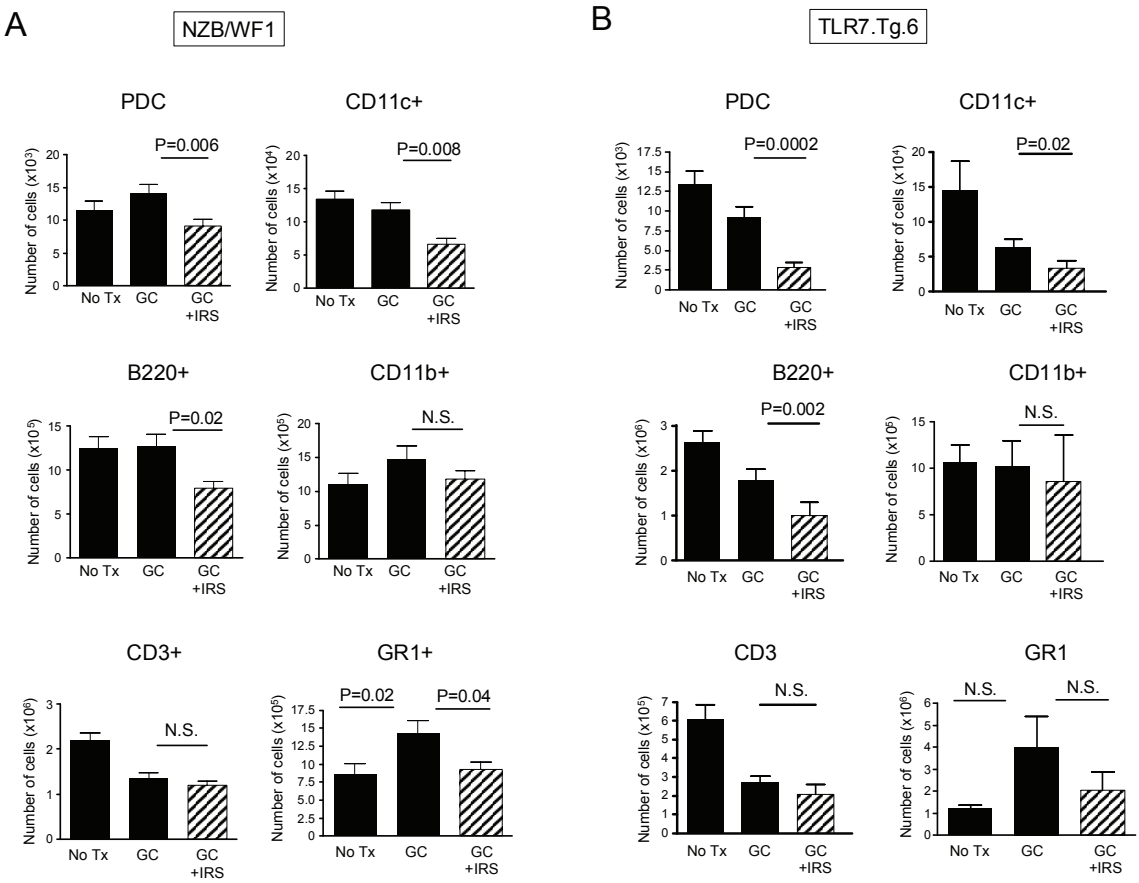
Supplementary Figure 3: GC do not affect TLR-induced p65 phosphorylation in PDC

Negatively purified PDC were either left untreated or cultured with CpG-C ISS (0.5 μM) (A), Flu (2 MOI) (B) either alone or in the presence of GC (10^{-5}M) or NF-kB inhibitor IKK-2 (0.5 μM) for 90 min after which cells were fixed immediately permabilized with PermBuffer III for 30 minutes on ice and stained with either Alexa-647 anti-human NF-kB p65 (pS529) (BD bioscience) and then analyzed by flow cytometry. Representative histograms of at least three separate experiments.



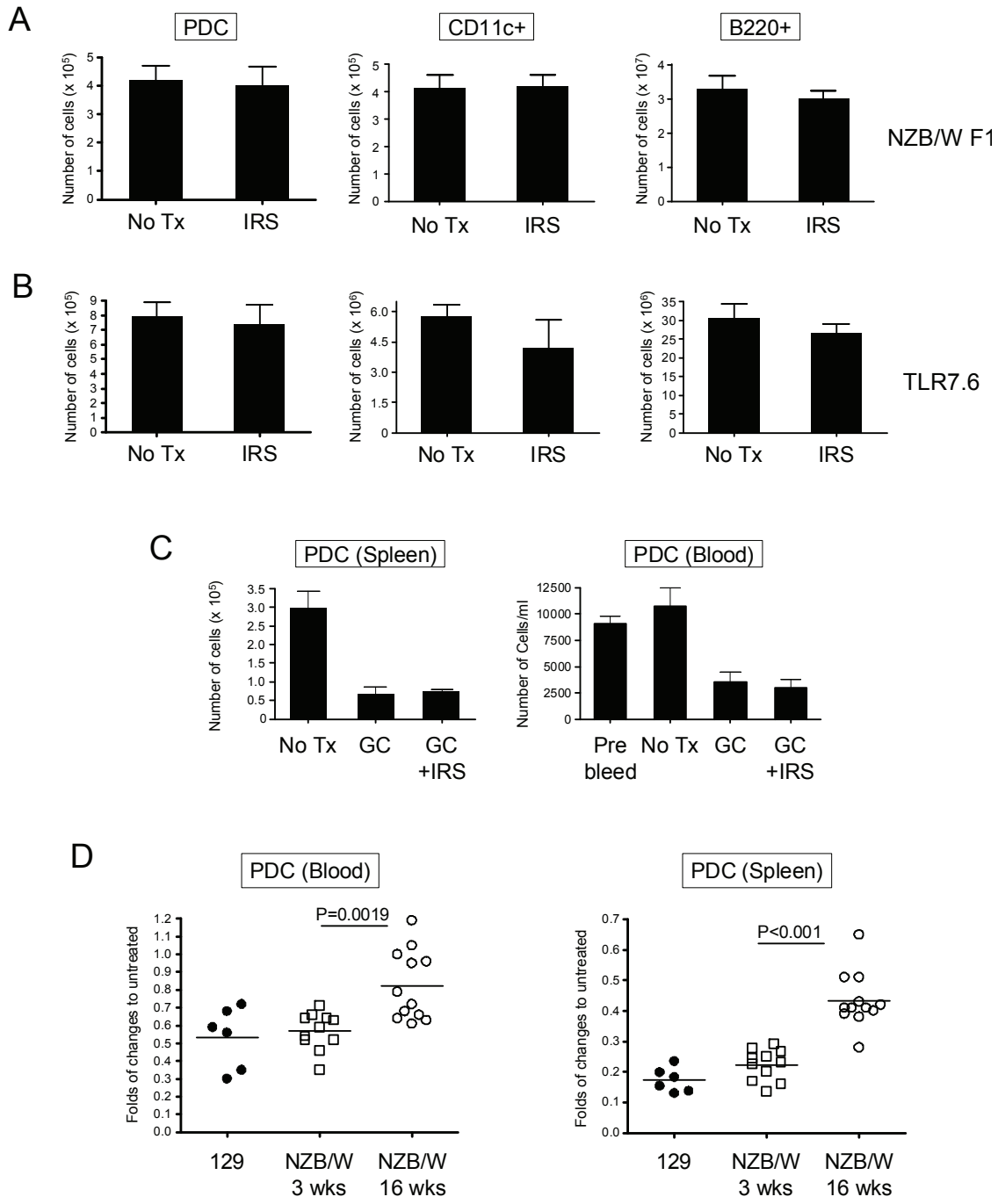
Supplementary Figure 4: IRS significantly reduce CpG-C ISS-mediated induction of cytokines *in vivo*

129 mice were either left untreated or treated with CpG-C ISS (50 μg/mice) alone or with IRS (50 μg/mice) and serum was collected 6 hr later. IFN-α and IL-6 was evaluated by ELISA. *n*=6 mice per group ± standard error of the mean.



Supplementary Figure 5: Increased resistance of PDC in lupus-prone mice is due to TLR7&9 stimulation

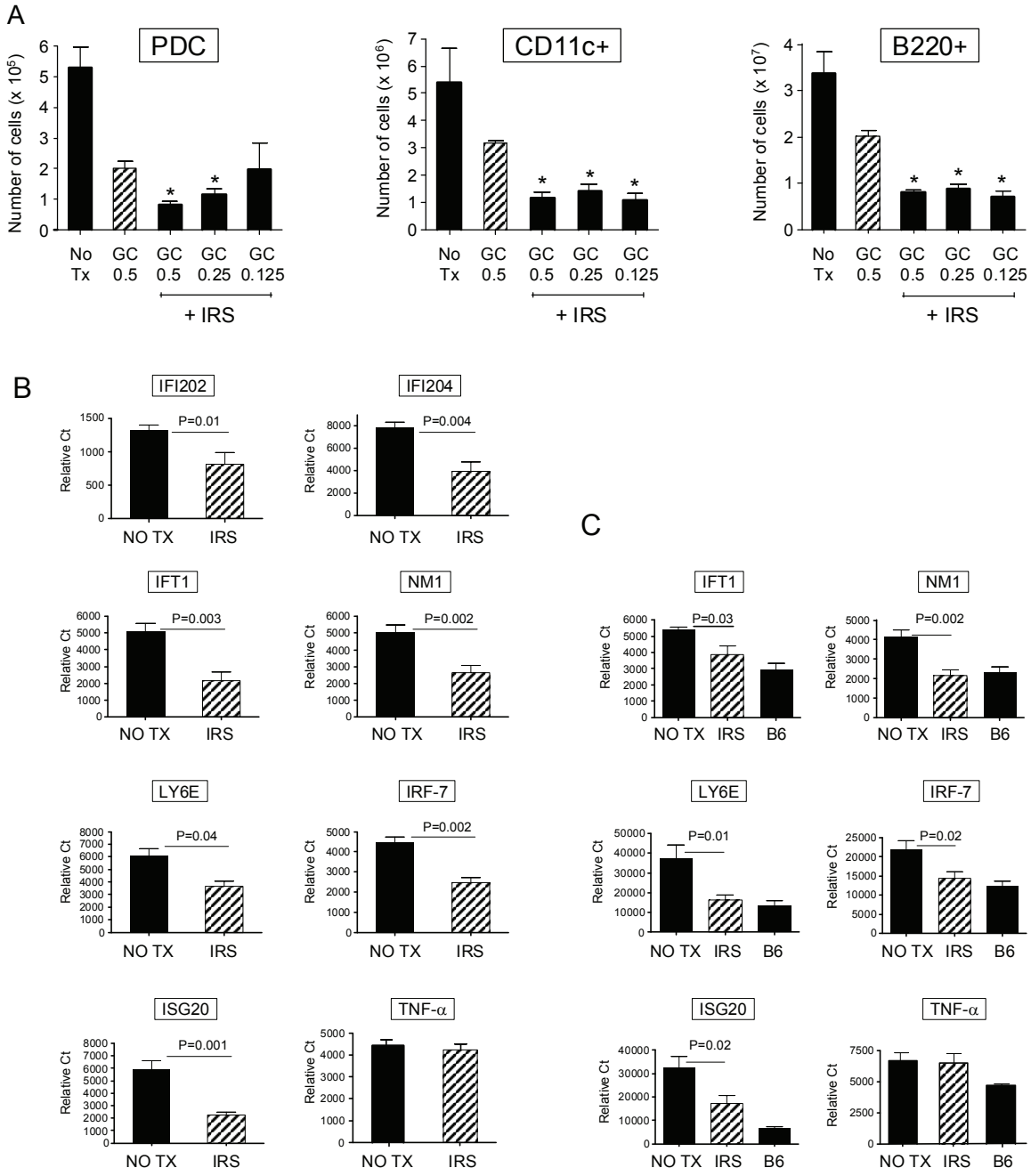
(A) (NZBxNZW)F_1 and (B) TLR7.Tg.6 mice were left untreated or treated with GC (0.5 mg) alone or with IRS . IRS (100 μg/mice s.c.) was administered every 3 days for 10 days prior to the GC treatment. Viability of the different cell subsets was assessed 18 hr after the injection of GC. Data refers to cell number/ml in the blood. Cumulative data ± standard error of the mean of two independent experiments n= 8-12 mice/group.



Supplementary Figure 6: Treatment of lupus-prone mice with TLR inhibitors does not affect viability in vivo in absence of GC in lupus-prone mice and does not have any effect on GC-treated WT mice. Resistance of PDC to GC-induced cell death in lupus mice require cellular activation.

(A) (NZBxNZW)F_1 or (B) TLR7.Tg.6 were either left untreated or treated every 3 days for 10 days with IRS (100 μg/mice s.c.) and the cell number was measured by flow cytometry in

the spleen 18 hr after last IRS administration. Data refers to the average ± standard error of the mean of the total cell number in spleens *n*=6 mice per group. Similar data were obtained in the blood stream (not shown). (C) 129 mice were left untreated or treated with GC 0.5 mg or GC plus IRS (100 μg/mice s.c.) as described in figure 4. Viability of PDC was assessed 18 hr after the injection of GC .*n*=6 mice per group. (D) 129 or the (NZBxNZW)F_1 lupus-prone animals (3 weeks or 16 weeks old) were either left untreated or treated with GC as in figure 4. Here, the dose of GC was adjusted based on weight of mice and 3 weeks old mice received 0.25 mg while adult mice received 0.5 mg. PDC cell numbers in blood and spleens was assessed 18 hr later. Data are expressed as fold of change to untreated mice for each mouse.



Supplementary Figure 7: Treatment of lupus-prone mice with TLR inhibitors reduces levels of IFN-inducible genes

(A) (NZBxNZW)F_1 mice were treated as described in figure 4 but when mice received IRS, we used different doses of GC (in mg per mouse here) (B) (NZBxNZW)F_1 and (C) TLR7.Tg.6 mice were left untreated or treated with IRS (100 μg/mice s.c) every 3 days for 10 days and spleens were harvested 18 hr after the last IRS injection. RNA was prepared from the spleens of the animals and the levels of type I IFN-regulated genes were measured by quantitative analysis (Taqman).Averages ± standard error of the mean for *n*=6-10 mice per group.

Supplementary Table 1

IFN Module Gene list

Probe ID	Gene Symbol	Entrez gene	Description
1010242	BATF2	116071	Basic leucine zipper transcription factor, ATF-like 2 (BATF2)
5720438	CMPK2	129607	Cytidine monophosphate (UMP-CMP) kinase 2, mitochondrial (CMPK2), nuclear gene encoding mitochondrial protein
7380544 *	CXCL10	3627	Chemokine (C-X-C motif) ligand 10 (CXCL10)
1260681	DDX60	55601	DEAD (Asp-Glu-Ala-Asp) box polypeptide 60 (DDX60)
6200273	EPSTI1	94240	Epithelial stromal interaction 1 (breast) (EPSTI1), transcript varian 2
1710259 *	HERC5	51191	Hect domain and RLD 5 (HERC5)
4280725	HES4	57801	Hairy and enhancer of split 4 (Drosophila) (HES4)
5870221 *	IFI44	10561	Interferon-induced protein 44 (IFI44)
7200255	IFI44L	10964	Interferon-induced protein 44-like (IFI44L)
1780632	IFIT1	3434	Interferon-induced protein with tetratricopeptide repeats 1 (IFIT1), transcript variant 2
6220673 *	IFIT1	3434	Interferon-induced protein with tetratricopeptide repeats 1 (IFIT1), transcript variant 2
430021	IFIT3	3437	Interferon-induced protein with tetratricopeptide repeats 3 (IFIT3)
2690452 *	IFIT3	3437	Interferon-induced protein with tetratricopeptide repeats 3 (IFIT3)
3830041	IFIT3	3437	Interferon-induced protein with tetratricopeptide repeats 3 (IFIT3)
4210291	IFITM3	10410	Interferon induced transmembrane protein 3 (1-8U) (IFITM3)
1070528 *	ISG15	9636	ISG15 ubiquitin-like modifier (ISG15)
1500204	LAMP3	27074	Lysosomal-associated membrane protein 3 (LAMP3)
5810709	LOC26010	26010	Viral DNA polymerase-transactivated protein 6 (LOC26010), transcript variant 2
2940022 *	LY6E	4061	Lymphocyte antigen 6 complex, locus E (LY6E)
2630110	MX1	4599	Myxovirus (influenza virus) resistance 1, interferon-inducible protein p78 (mouse) (MX1)

3940731	OAS1	4938	2',5'-oligoadenylate synthetase 1, 40/46kda (OAS1), transcript variant 3
4040632	OAS1	4938	2',5'-oligoadenylate synthetase 1, 40/46kda (OAS1), transcript variant 2
6560494 *	OAS1	4938	2',5'-oligoadenylate synthetase 1, 40/46kda (OAS1), transcript variant 1
1240754	OAS2	4939	2'-5'-oligoadenylate synthetase 2, 69/71kda (OAS2), transcript variant 1
7330373 *	OAS2	4939	2'-5'-oligoadenylate synthetase 2, 69/71kda (OAS2), transcript variant 2
4220435 *	OAS3	4940	2'-5'-oligoadenylate synthetase 3, 100kda (OAS3)
6370035 *	OASL	8638	2'-5'-oligoadenylate synthetase-like (OASL), transcript variant 2
7150196	OASL	8638	2'-5'-oligoadenylate synthetase-like (OASL), transcript variant 1
3710184 *	OTOF	9381	Otoferlin (OTOF), transcript variant 4
6620711	RSAD2	91543	Radical S-adenosyl methionine domain containing 2 (RSAD2)
770364	RTP4	64108	Receptor (chemosensory) transporter protein 4 (RTP4)
4390575	SERPING1	710	Serpin peptidase inhibitor, clade G (C1 inhibitor), member 1, (angioedema, hereditary) (SERPING1), transcript variant 2
380386	TRIM6	117854	Tripartite motif-containing 6 (TRIM6), transcript variant 2
1740341	XAF1	54739	XIAP associated factor 1 (XAF1), transcript variant 2
940673			Erythroid Precursor Cells (LCB:cl library) cdna clone cl02h05 5
6900603			AGENCOURT_7914287 NIH_MGC_71 cdna clone IMAGE:6156595 5, mrna sequence

* Probes in Nanostring Codeset

Supplementary Table 2

Patient information

Subject	Ethic	Gender	Age
SLE-20	AA	Female	16
SLE-29	Hispanic	Male	16
SLE-31	Hispanic	Female	12
SLE-33	Asian	Female	11
SLE-34	Hispanic	Female	16
SLE-40	AA	Female	15
SLE-55	AA	Female	16
SLE-60	Hispanic	Female	15
SLE-64	White	Female	16
SLE-79	Hispanic	Female	14
SLE-80	AA	Female	16
SLE-83	AA	Female	15
SLE-87	White	Female	17
SLE-91	Asian	Female	14
SLE-95	AA	Female	17
SLE-110	AA	Female	15
SLE-121	Hispanic	Female	15
SLE-123	Hispanic	Male	13
SLE-125	Hispanic	Female	15
SLE-128	AA	Female	16
SLE-141	Hispanic	Male	14
SLE-142	White	Female	17
SLE-143	Hispanic	Female	15
SLE-144	White	Female	14
SLE-154	Hispanic	Male	13
SLE-157	AA	Female	17
SLE-158	Hispanic	Female	17
SLE-163	White	Female	11
SLE-168	Hispanic	Female	17
SLE-169	Hispanic	Female	14
SLE-171	Hispanic	Female	13
SLE-172	Hispanic	Female	11
SLE-175	White	Female	12
SLE-179	Hispanic	Female	13

SLE-181	Hispanic	Female	12
SLE-182	Hispanic	Male	15
SLE-183	Hispanic	Female	11
SLE-184	AA	Female	7
SLE-185	Asian	Female	13
SLE-186	Asian	Female	18
SLE-187	Hispanic	Female	13
SLE-188	Hispanic	Female	12
SLE-189	AA	Female	14
SLE-191	AA	Female	16
SLE-192	Hispanic	Male	16
SLE-196	AA	Female	14
SLE-198	AA	Male	18
SLE-208	AA	Female	14
SLE-212	AA	Female	14
SLE-213	White	Female	12
SLE-214	Hispanic	Female	16
SLE-215	Other	Female	12
SLE-216	White	Male	12
SLE-225	Hispanic	Female	16
SLE-226	Asian	Male	15
SLE-229	AA	Female	17
SLE-231	AA	Female	17
SLE-233	White	Female	11
SLE-237	Hispanic	Female	12
SLE-238	White	Female	17
SLE-240	Hispanic	Female	15
SLE-241	AA	Female	13
SLE-242	Hispanic	Female	10
SLE-244	Hispanic	Female	9
SLE-249	AA	Male	9
SLE-252	AA	Female	14
SLE-260	AA	Female	12
SLE-270	Asian	Female	14
SLE-276	White	Male	12
SLE-277	Hispanic	Female	17
SLE-282	AA	Female	17