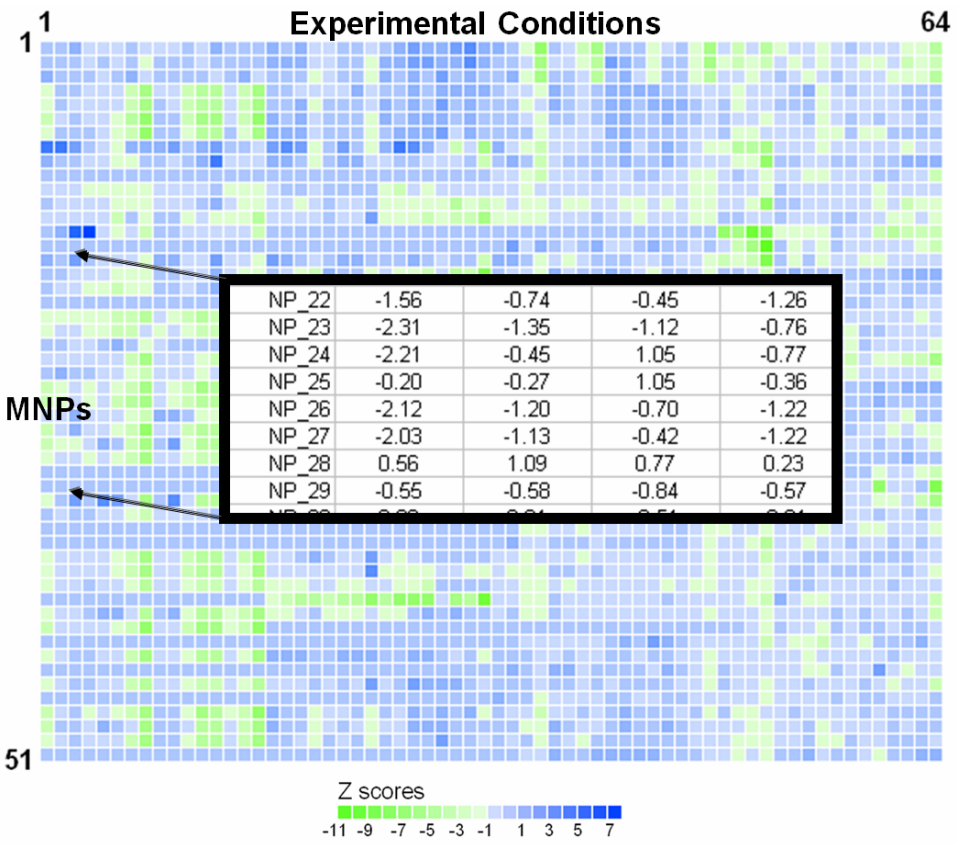

Figure S1. Activity Heat Map of the biological responses induced by 51 MNPs tested against four cell lines at four different concentrations using four different assays [based on data from reference *(26)*], representing 64 experimental conditions (dose, cell line, assay).

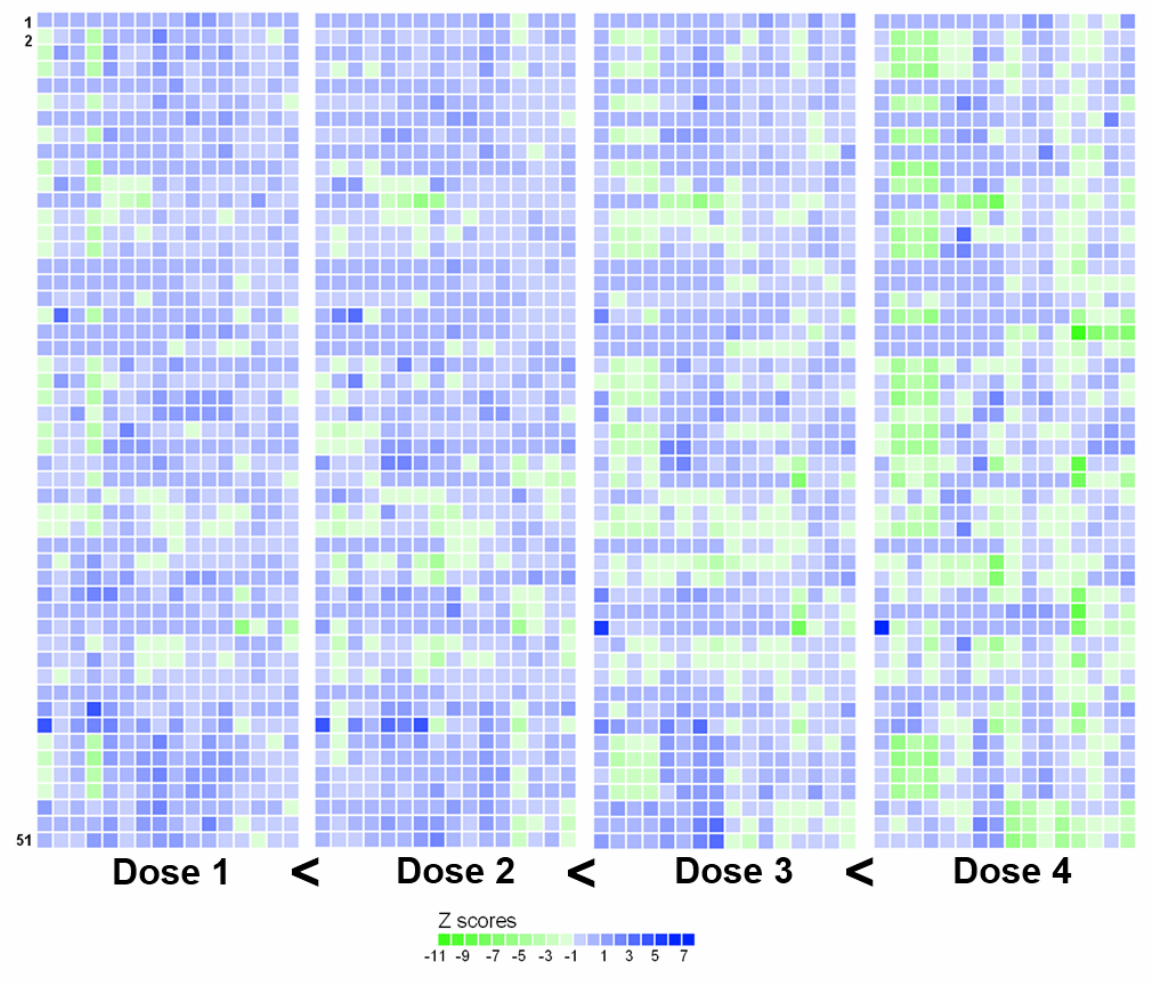

Figure S2. Influence of MNP concentration on their induced biological activity profiles *[doses 1-4 are equal to 0.01, 0.03, 0.1 and 0.3 Fe (mg/ml) for iron-based nanoparticles (NP_1-48) respectively; for the three quantum dot-based nanoparticles (NP_49-51), concentrations were equal to 1, 3, 30 and 100 nM]*.

Table S1. Case Study 1 – QNAR classification modeling of 44 MNPs using four experimental descriptors (size, relaxivities R1 and R2, zeta potential). The overall biological activity induced by a given nanoparticle was calculated as the average of all activity (expressed as Z_{mean} scores – see text for details) for all 64 conditions (dose/cell line/assay); the classification cutoff is equal to Z_{mean} = -0.4 to obtain a balanced dataset (22 nanoparticles in class 1, 22 particles in class 0). External predictions from the 5-fold Cross-Validation procedure are given in the column "Predicted Class".

IDs	Experimental Descriptors				Mean Z score (Z_{mean})	Clusters	Class	Predicted Class
	Size (nm)	R1	R2	Zeta potential				
NP_1	36	19	45	-19.9	0.20	1	**1**	1
NP_2	30	26	74	-9.22	-0.50	2	**0**	0
NP_3	32	21	54	5.9	-0.30	2	**1**	1
NP_4	74	21	153	-2.72	-0.51	2	**0**	1
NP_5	27	17	36	3.34	-0.09	1	**1**	0
NP_6	29	22	51	1.95	-0.40	2	**1**	0
NP_7	38	21	62	-10.1	0.01	1	**1**	0
NP_8	33	22	49	-19.5	-0.38	2	**1**	1
NP_9	36	19	45	-14	-0.07	1	**1**	1
NP_10	28	19	39	3.24	-0.61	2	**0**	0
NP_11	31	23	59	-9.46	-0.59	2	**0**	0
NP_12	31	19	49	3.64	-1.31	3	**0**	0
NP_14	28	19	39	2.34	-0.85	2	**0**	0
NP_15	24	22	54	-11.7	-0.64	2	**0**	0
NP_16	37	21	52	0.766	-0.07	1	**1**	1
NP_17	38	21	62	-20.7	-0.31	3	**1**	1
NP_18	38	21	62	-9.08	-0.21	1	**1**	0
NP_19	31	19	49	-3.61	-0.49	2	**0**	0
NP_20	38	21	62	-9.34	-0.50	1	**0**	1
NP_21	28	15	40	-9.23	-0.47	3	**0**	0
NP_22	36	36	122	-21.9	-0.35	2	**1**	1
NP_23	31	20	45	-6.11	-0.62	2	**0**	0
NP_26	40	15	30	-12	-0.68	2	**0**	1
NP_27	40	15	30	-3.77	-0.03	2	**1**	0
NP_28	40	15	30	-7.57	-0.46	1	**0**	0
NP_29	40	15	30	0.25	-0.89	1	**0**	0
NP_30	40	15	30	-6.05	-0.49	3	**0**	0
NP_31	20	0.5	0.5	-12.3	-0.89	3	**0**	0
NP_32	20	0.5	0.5	-4.22	-1.15	3	**0**	0
NP_33	20	0.5	0.5	-7.15	-0.99	3	**0**	0
NP_34	20	0.5	0.5	-4.3	-0.35	3	**1**	0
NP_35	20	0.5	0.5	-12.1	-0.23	3	**1**	1
NP_36	20	0.5	0.5	-15.6	-0.32	1	**1**	1
NP_37	20	0.5	0.5	-16.1	-0.56	1	**0**	0
NP_38	20	0.5	0.5	-4.7	-0.82	1	**0**	0
NP_39	20	0.5	0.5	-6.47	-0.93	3	**0**	0
NP_40	20	0.5	0.5	-6.54	-0.64	3	**0**	0
NP_41	20	0.5	0.5	-10.8	-0.33	3	**1**	0
NP_42	20	0.5	0.5	-7.7	0.04	3	**1**	0
NP_43	20	0.5	0.5	-6.75	0.14	1	**1**	0
NP_45	23	29	62	-13.6	-0.25	2	**1**	1
NP_46	33	36	106	-14.5	-0.33	2	**1**	1
NP_47	28	32	60	-9.23	-0.21	2	**1**	1
NP_48	25	29	49	-37	-0.25	2	**1**	1

Table S2. Case Study 2 – PaCa2 cell uptake for 109 MNPs with different surface modifiers.

IDs	SMILES strings	PaCa2 cellular uptake (log_{10} [nanoparticles]/cell pM)
1	FC(F)(F)C(=O)OC(=O)C(F)(F)F	4.17
2	FC(F)(Cl)C(=O)OC(=O)C(F)(F)Cl	3.95
3	FC(F)(F)C(F)(F)C(=O)OC(=O)C(F)(F)C(F)(F)F	4.08
4	CC1(C)CC(=O)OC1=O	4.11
5	O=C1OC(=O)C=C1	3.98
6	CC1=CC(=O)OC1=O	3.58
7	CC1=C(C)C(=O)OC1=O	3.48
8	CCCCCC(=O)OC(=O)CCCCC	3.65
9	CC1CC(=O)OC1=O	3.64
10	O=C1OC(=O)c2cc(ccc12)C(=O)c1ccc2C(=O)OC(=O)c2c1	3.51
11	O=C1OC(=O)c2cc(ccc12)N(=O)=O	3.27
12	Brc1ccc2C(=O)OC(=O)c3cccc1c23	3.63
13	O=C1OC(=O)c2ccc3C(=O)OC(=O)c4ccc1c2c34	3.67
14	Fc1c(F)c(F)c2C(=O)OC(=O)c2c1F	3.83
15	O=C1OC(=O)c2cc(cc3cccc1c23)N(=O)=O	4.11
16	Oc1cccc2C(=O)OC(=O)c12	3.97
17	O=C1OC(=O)C2C3CCC(C=C3)C12	3.90
18	Clc1ccc2NC(=O)OC(=O)c2c1	4.18
19	O=C1OS(=O)(=O)c2ccccc12	3.88
20	ClC1=C(Cl)C(=O)OC1=O	3.84
21	CC(=O)SC1CC(=O)OC1=O	3.59
22	Clc1cc2C(=O)OC(=O)c2cc1Cl	4.12
23	O=C1OC(=O)C2C3OC(C=C3)C12	3.82
24	O=C1OC(=O)C2C3C=CC(C12)C1C3C(=O)OC1=O	3.63
25	O=C1OC(=O)C2CC=CCC12	3.89
26	O=C1OC(=O)c2ccccc2-c2ccccc12	3.77
27	O=C1OC(=O)c2ccc(c3cccc1c23)N(=O)=O	3.93
28	O=C1OC(=O)C2C1C1C2C(=O)OC1=O	3.77
29	CCCCCCCCCCCCC(=O)OC(=O)CCCCCCCCCCCC	3.82
30	OC(=O)c1ccc2C(=O)OC(=O)c2c1	3.55
31	Cc1ccc2C(=O)OC(=O)c2c1	3.98
32	O=C1OC(=O)c2c1cccc2N(=O)=O	3.50
33	O=C1Cc2ccccc2C(=O)O1	3.78
34	O=C1CCCC(=O)O1	4.07
35	O=C1CN(CCN2CC(=O)OC(=O)C2)CC(=O)O1	3.93
36	O=C1Nc2ccccc2C(=O)O1	4.44
37	CN1C(=O)OC(=O)c2ccccc12	3.36
38	CC1CC(=O)OC(=O)C1	3.91
39	O=C1OC(=O)C2=C1CCCC2	3.73
40	CC(=O)OC1C(OC(C)=O)C(=O)OC1=O	3.91
41	Brc1c(Br)c(Br)c2C(=O)OC(=O)c2c1Br	3.80
42	O=C1OC(=O)C2CCCCC12	3.93
43	O=C1OC(=O)C2=C1CCC2	3.69
44	ICC(=O)OC(=O)CI	3.42
45	ClCC(=O)OC(=O)CCl	3.63
46	ClC1=C(Cl)C2(Cl)C3C(C(=O)OC3=O)C1(Cl)C2(Cl)Cl	3.47
47	CCCCCCCCCCCCCCCCC(=O)OC(=O)CCCCCCCCCCCCCCCC	3.55
48	Nc1ccc2C(=O)OC(=O)c3cccc1c23	3.64
49	CCCCCCCCCC(=O)OC(=O)CCCCCCCCC	4.03
50	O=C1CC2(CCCC2)CC(=O)O1	4.06
51	O=C1OC(=O)C2C3CCC(C3)C12	3.94
52	O=C1OC(=O)c2cccc3cccc1c23	3.96
53	O=C1CCC(C(=O)O1)c1ccccc1	4.02

54	Clc1c(Cl)c(Cl)c2C(=O)OC(=O)c2c1Cl	3.83
55	Clc1ccc(Cl)c2C(=O)OC(=O)c12	3.90
56	CC1(C)CCC(=O)OC1=O	3.94
57	CCCCCN	3.78
58	CC(C)CC(C)N	3.85
59	NC1C(O)CC(CO)C(O)C1O	3.36
60	CCCCCCN	3.75
61	CC(C)(C)N	3.86
62	CC(C)CN	3.72
63	CC(C)(C)CN	3.75
64	CC(C)CCN	3.83
65	CCC(N)CC	3.81
66	CCC(C)(C)N	4.07
67	NCCN	3.46
68	CCCCCCCCCCCCCCCN	4.06
69	NCCCN	3.49
70	NCCCCN	3.48
71	NCCCCCCN	3.62
72	CCCCC(CC)CN	3.95
73	CCCCCCCCCCCCCCCCCN	3.97
74	CCCCCC(C)N	3.63
75	CCCCCCCCCCCCCCCN	4.27
76	NCCNCCN	3.77
77	NCC12CC3CC(CC(C3)C1)C2	2.84
78	NCCc1ccc(O)c(O)c1	2.53
79	NCCc1ccc(O)cc1	2.77
80	NCCCNCCCCNCCN	2.41
81	NCCNCCCNCCN	2.23
82	NCCNCCNCCNCCNCCN	2.54
83	NC12CC3CC(CC1C3)C2	3.12
84	NC1C2CC3CC(C2)CC1C3	3.18
85	NCC(O)=O	2.57
86	COC(=O)C(N)Cc1ccccc1	3.39
87	NC(CO)C(O)=O	3.36
88	CC(O)C(N)C(O)=O	3.21
89	NC(Cc1c[nH]c2ccccc12)C(O)=O	3.19
90	NC(Cc1ccc(O)cc1)C(O)=O	3.07
91	CC(C)C(N)C(O)=O	3.27
92	NCCCCC(N)C(O)=O	3.25
93	NC(C(O)=O)c1ccc(Cl)cc1	3.06
94	CC(N)C(O)=O	2.90
95	NC(CCCNC(N)=N)C(O)=O	3.15
96	NC(CC(O)=O)C(O)=O	3.29
97	NC(CCC(N)=O)C(O)=O	3.32
98	NC(CCC(O)=O)C(O)=O	3.40
99	NC(Cc1c[nH]cn1)C(O)=O	3.38
100	CSCCC(N)C(O)=O	3.23
101	NC(Cc1ccccc1)C(O)=O	3.29
102	O=C1CCC(=O)O1	4.24
103	CC(=O)OC(C)=O	4.05
104	C=C1CC(=O)OC1=O	4.04
105	O=C1COCC(=O)O1	3.99
106	O=C1OC(=O)c2ccccc12	3.90
107	OC(=O)CC1CC(=O)OC1=O	4.03
108	Fc1ccc(F)c2C(=O)OC(=O)c12	3.91
109	OC(=O)CN(CCN1CC(=O)OC(=O)C1)CCN1CC(=O)OC(=O)C1	4.10

Table S3. Top-10 selected descriptors for each modeling fold according to their model frequency.

Fold 1		Fold 2		Fold 3		Fold 4		Fold 5	
Descriptor Name	**Freq.**	**Descriptor Name**	**Freq.**	**Descriptor Name**	**Freq.**	**Descriptor Name**	**Freq.**	**Descriptor Name**	**Freq.**
vsa_other	0.28	SlogP_VSA5	0.26	PEOE_VSA+1	0.38	SlogP_VSA1	0.29	SlogP_VSA2	0.32
PEOE_VSA+1	0.27	PEOE_VSA-2	0.23	SlogP_VSA0	0.22	SlogP_VSA2	0.23	SlogP_VSA1	0.28
SlogP_VSA5	0.26	SlogP_VSA1	0.21	PEOE_VSA_FPOS	0.19	SlogP_VSA5	0.21	SlogP_VSA0	0.23
b_double	0.24	PEOE_VSA_FPOS	0.20	SlogP_VSA5	0.16	SMR_VSA4	0.19	b_double	0.21
SlogP_VSA1	0.21	GCUT_SLOGP_0	0.19	a_nN	0.16	BCUT_PEOE_3	0.19	VAdjEq	0.20
vsa_don	0.18	GCUT_SMR_1	0.19	PEOE_VSA_FNEG	0.16	vsa_don	0.17	zagreb	0.20
GCUT_PEOE_1	0.16	BCUT_SLOGP_1	0.17	BCUT_PEOE_1	0.15	BCUT_SLOGP_1	0.15	VDistMa	0.17
SlogP_VSA2	0.15	SlogP_VSA2	0.17	SlogP_VSA1	0.15	SMR_VSA2	0.15	PEOE_PC-	0.17
GCUT_SMR_1	0.14	b_double	0.17	BCUT_SLOGP_1	0.14	GCUT_PEOE_2	0.14	VAdjMa	0.17
GCUT_SMR_0	0.13	BCUT_SLOGP_0	0.17	b_double	0.14	PEOE_VSA_FPOS	0.14	chi0v_C	0.16

Table S4. Top-10 descriptors with the highest averaged frequency.

Descriptor Name	Avg. Freq.
SlogP_VSA1	0.23
SlogP_VSA2	0.19
SlogP_VSA5	0.18
b_double	0.18
SlogP_VSA0	0.16
PEOE_VSA+1	0.16
vsa_don	0.15
vsa_other	0.14
vsa_base	0.12
PEOE_VSA_FPOS	0.12