Figure 1

```
YFGKL ESKLS VIRNL NDQVL FIDQG NRPLF EDMTD SDCRD NAPRT IFIIS   50
MYKDS QPRGM AVTIS VKCEK ISTLS CENKI ISFKE MNPPD NIKDT KSDII  100
FFQRS VPGHD NKMQF ESSSY EGYFL ACEKE RDLFK LILKK EDELG DRSIM  150
FTVQN ED   157
```

Figure 2

```
NFGRL HCTTA VIRNI NDQVL FVDKR QPVFE DMTDI DQSAS EPQTR LIIYM  50
YKDSE VRGLA VTLSV KDSKM STLSC KNKII SFEEM DPPEN IDDIQ SDLIF 100
FQKRV PGHNK MEFES SLYEG HFLAC QKEDD AFKLI LKKKD ENGDK SVMFT 150
LTNLH QS  157
```

Figure 3

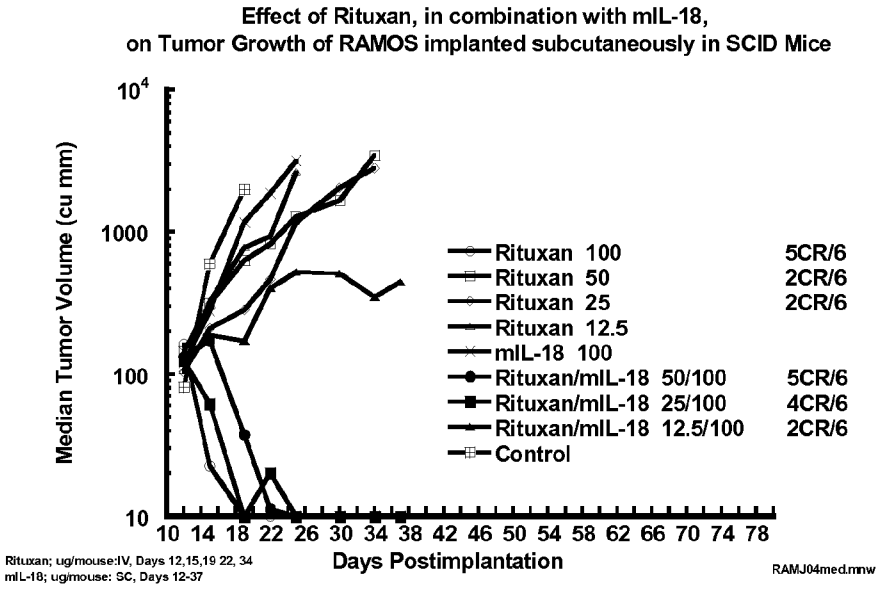
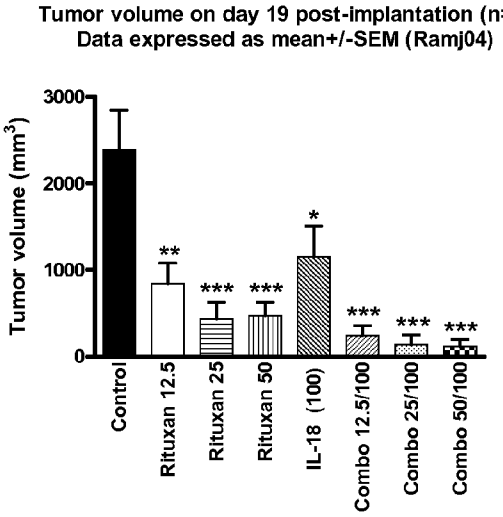
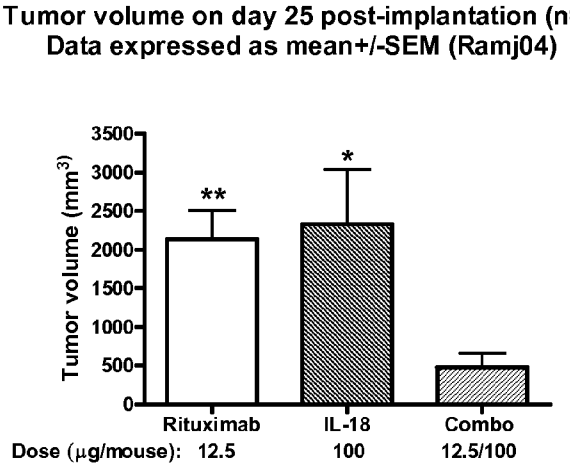

Effect of Rituxan, in combination with mIL-18,
on Tumor Growth of RAMOS implanted subcutaneously in SCID Mice
Median Tumor Volume (cu mm)
10^4
1000
100
10
10 14 18 22 26 30 34 38 42 46 50 54 58 62 66 70 74 78
Days Postimplantation
Rituxan 100 5CR/6
Rituxan 50 2CR/6
Rituxan 25 2CR/6
Rituxan 12.5
mIL-18 100
Rituxan/mIL-18 50/100 5CR/6
Rituxan/mIL-18 25/100 4CR/6
Rituxan/mIL-18 12.5/100 2CR/6
Control
Rituxan; ug/mouse:IV, Days 12,15,19 22, 34
mIL-18; ug/mouse: SC, Days 12-37
RAMJ04med.mnw

Figure 4



All treatment groups showed statistical significant decrease in tumor growth as compared to the untreated control group (*p<0.05, **p<0.01, ***p<0.001; One-way ANOVA followed by multiple comparison Bonferroni test).

Figure 5



The combinational therapy resulted in a statistically significant arrest of tumor growth as compared to the monotherapy with rituximab ($p<0.01$), or mIL-18 ($^*p<0.05$); unpaired t-test.

Figures 6A and 6B

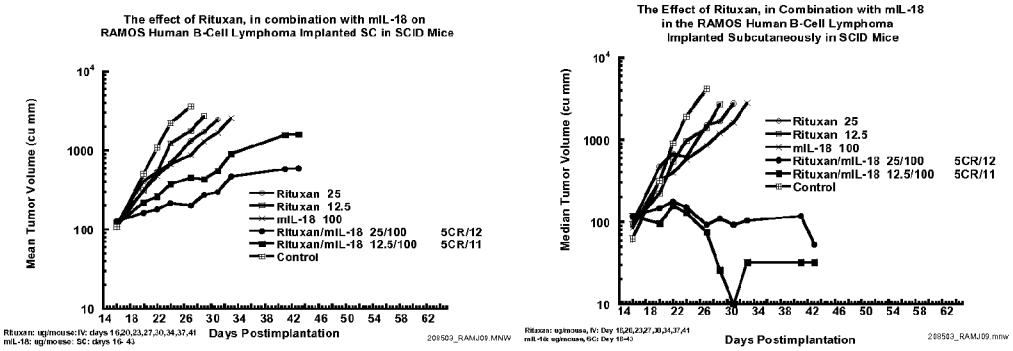
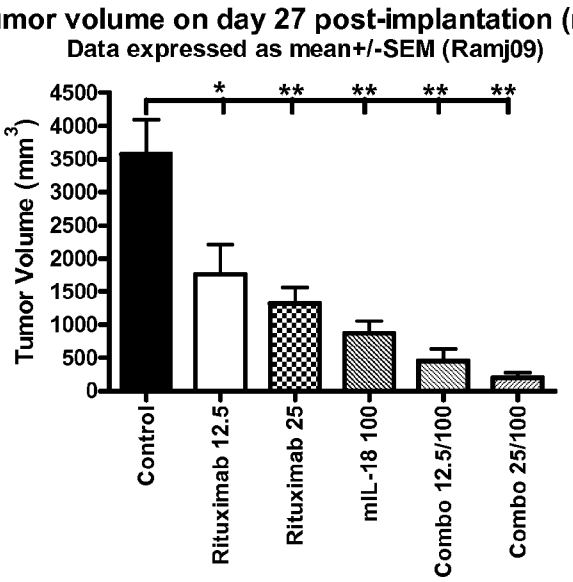
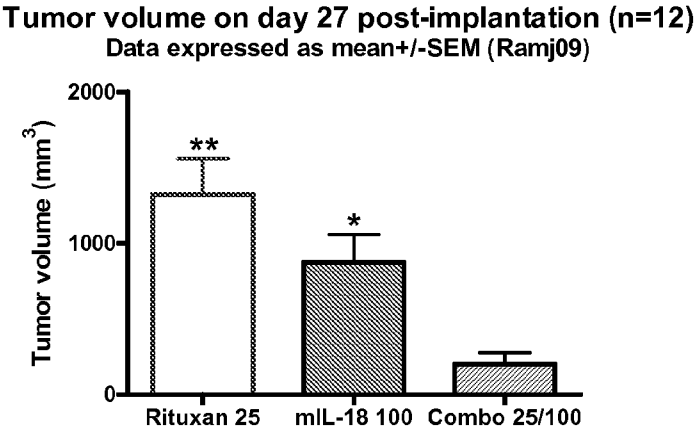


Figure 7



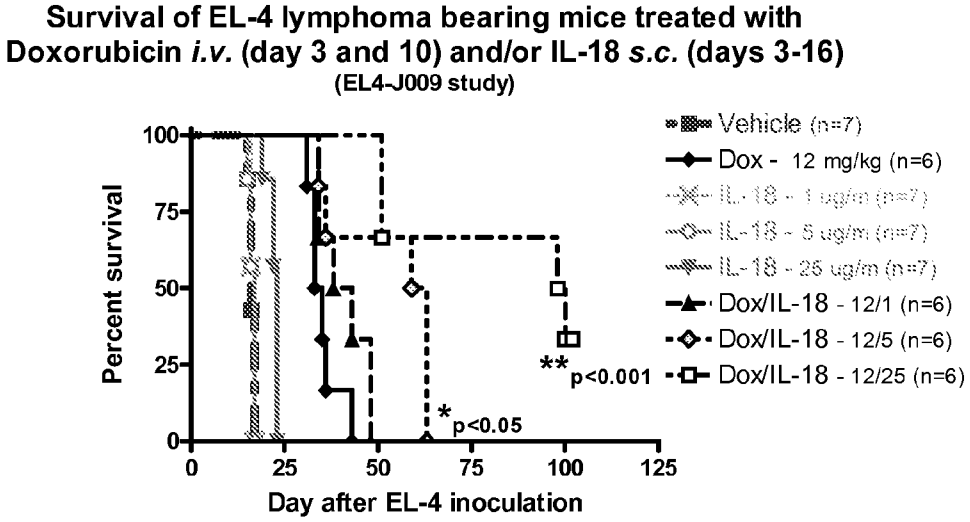
The graph shows statistically significant difference in all treatment groups as compared to the control group (one-way ANOVA with Bonferroni posttest (*p<0.01, **p<0.001)

Figure 8



The difference between the monotherapy groups and the combinational therapy group was statistically significant (*p<0.05, **p<0.001; one-way ANOVA followed by Tukey's posttest)

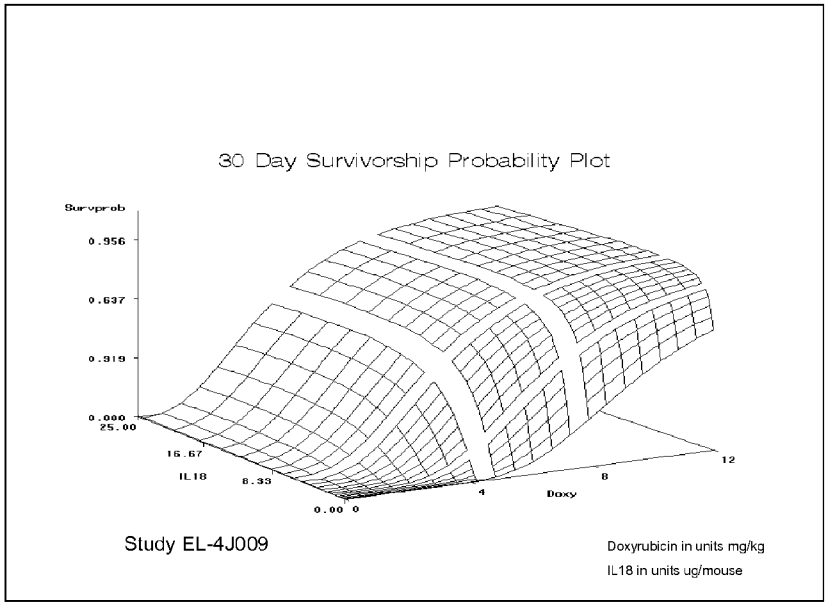
Figure 9



**p<0.001 - The survival of combination therapy group (Doxorubicin 12 mg/kg & IL-18 - 25 ug/m) was significantly better than survival of groups treated with Doxorubicin monotherapy (12 mg/kg), or IL-18 monotherapy (25 ug/m) or a vehicle.

*p<0.05 - The survival of combination therapy group (Doxorubicin 12 mg/kg & IL-18 - 5 ug/m) was significantly better than survival of groups treated with Doxorubicin monotherapy (12 mg/kg), or IL-18 monotherapy (5 ug/m; p<0.001) or a vehicle (p<0.001).
(The Kaplan-Meyer survival curve with Logrank test)

Figure 10


30 Day Survivorship Probability Plot
Survprob
0.956
0.637
0.319
0.000
25.00
16.67
IL18
8.33
0.00
0
4
Doxy
8
12
Study EL-4J009
Doxyrubicin in units mg/kg
IL18 in units ug/mouse

Figures 11A and 11B

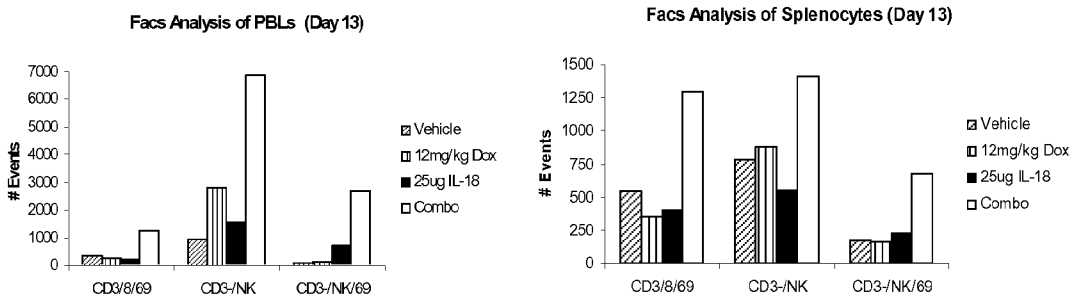


Figure 12

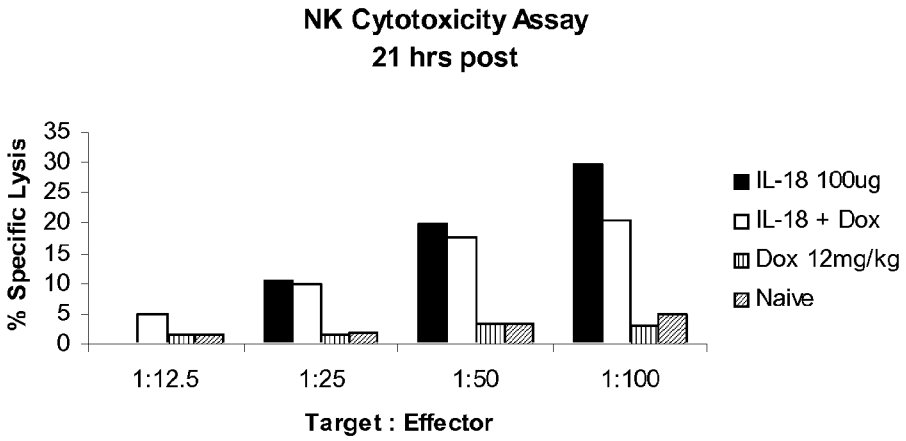

NK Cytotoxicity Assay
21 hrs post
% Specific Lysis
35
30
25
20
15
10
5
0
1:12.5
1:25
1:50
1:100
Target : Effector
IL-18 100ug
IL-18 + Dox
Dox 12mg/kg
Naive

Figure 13

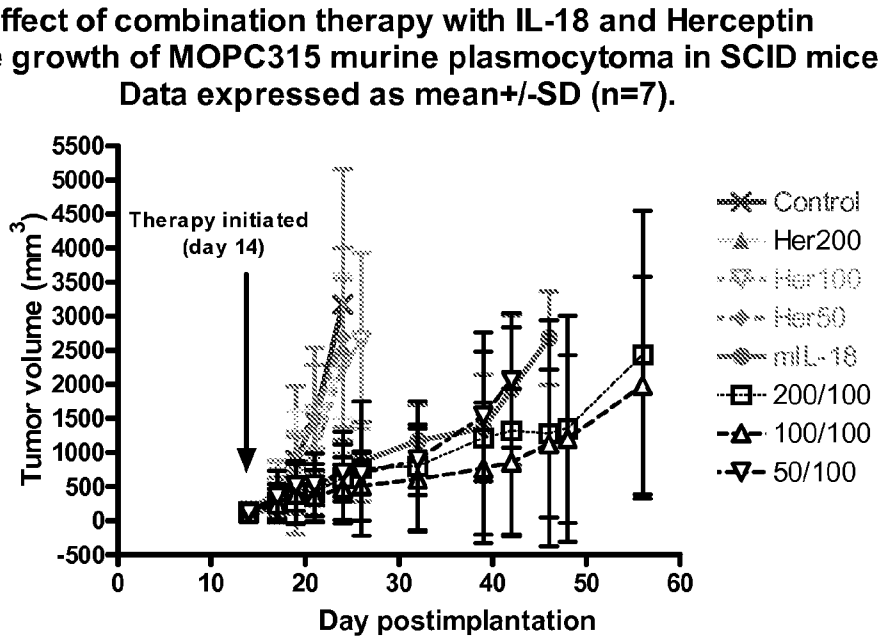

Effect of combination therapy with IL-18 and Herceptin
on the growth of MOPC315 murine plasmocytoma in SCID mice.
Data expressed as mean+/-SD (n=7).
Therapy initiated
(day 14)
Tumor volume (mm3)
Day postimplantation
Control
Her200
Her100
Her50
mIL-18
200/100
100/100
50/100

Figure 14

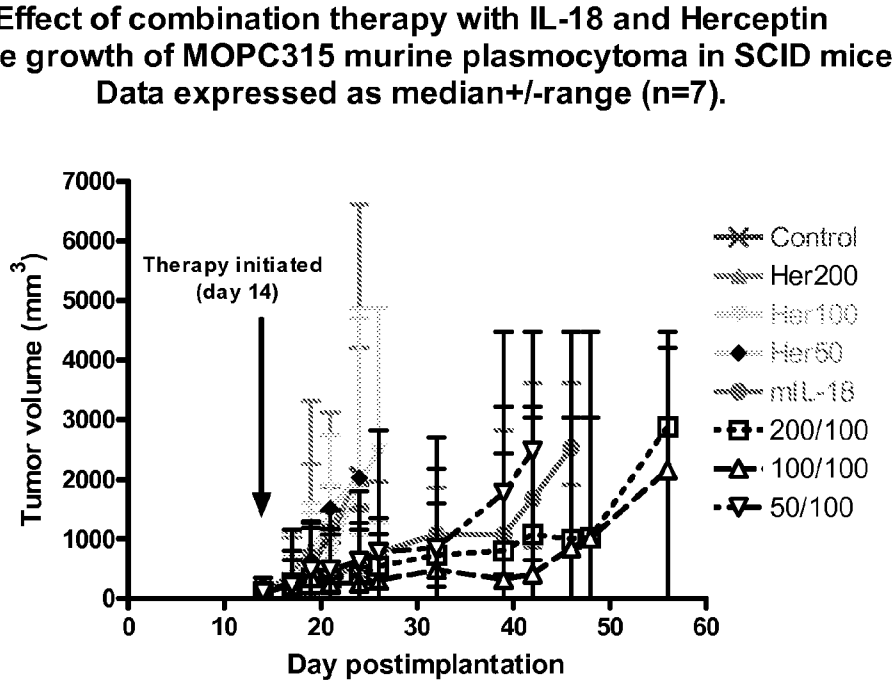
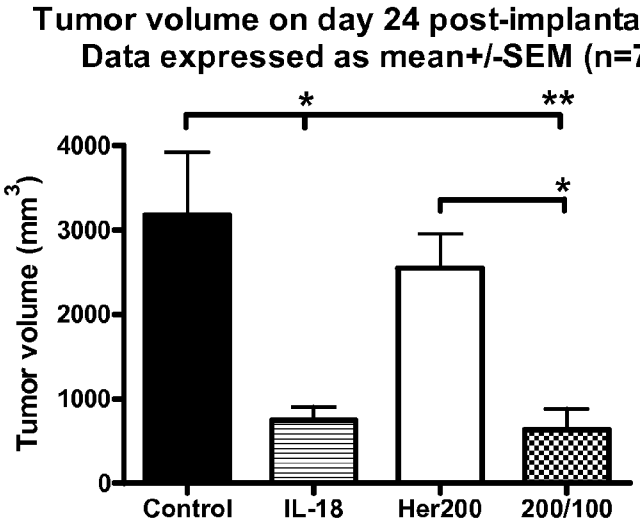
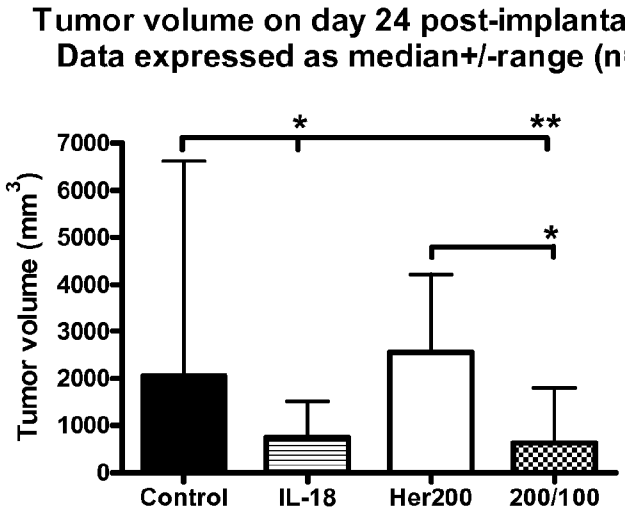

Effect of combination therapy with IL-18 and Herceptin
on the growth of MOPC315 murine plasmocytoma in SCID mice.
Data expressed as median+/-range (n=7).
Tumor volume (mm3)
Therapy initiated
(day 14)
Day postimplantation
Control
Her200
Her100
Her50
mIL-18
200/100
100/100
50/100
0
1000
2000
3000
4000
5000
6000
7000
0
10
20
30
40
50
60

Figure 15



Statistical difference was determined in the group treated with IL-18 alone, or with the IL-18 & Herceptin combinational therapy (as compared to the untreated control group). The combinational therapy was also significantly more effective than monotherapy with Herceptin (*$p<0.05$, **$p<0.01$; Kruskal-Wallis analysis with Dunn's multiple comparison test).

Figure 16



Statistical difference was determined in the group treated with IL-18 alone, or with the IL-18 & Herceptin combinational therapy (as compared to the untreated control group). The combinational therapy was also significantly more effective than monotherapy with Herceptin (*$p<0.05$, **$p<0.01$; Kruskal-Wallis analysis with Dunn's multiple comparison test).

Figure 17

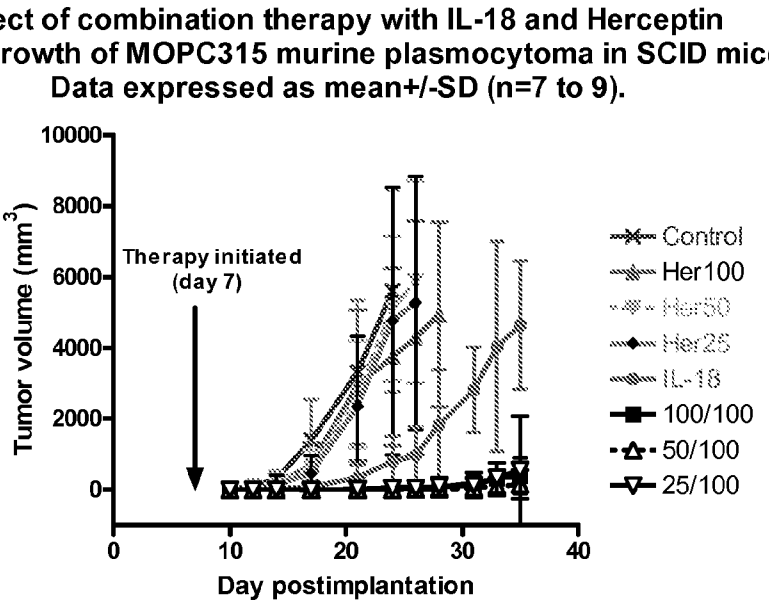

Effect of combination therapy with IL-18 and Herceptin
on the growth of MOPC315 murine plasmocytoma in SCID mice.
Data expressed as mean+/-SD (n=7 to 9).
Tumor volume (mm3)
10000
8000
6000
4000
2000
0
Therapy initiated
(day 7)
0
10
20
30
40
Day postimplantation
Control
Her100
Her50
Her25
IL-18
100/100
50/100
25/100

Figure 18

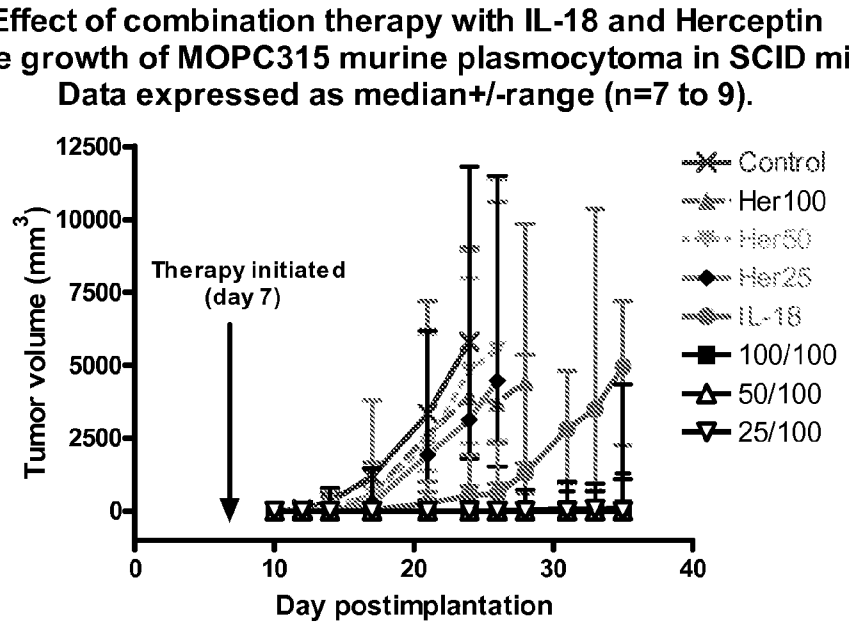
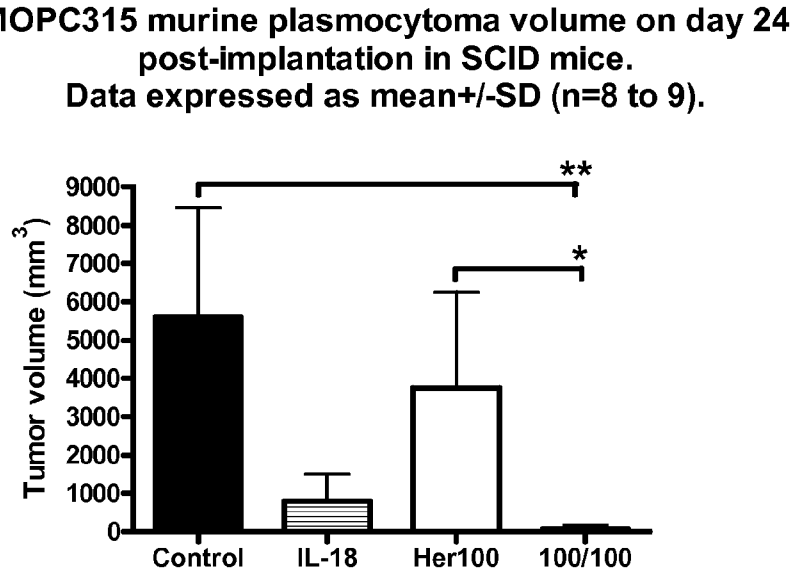
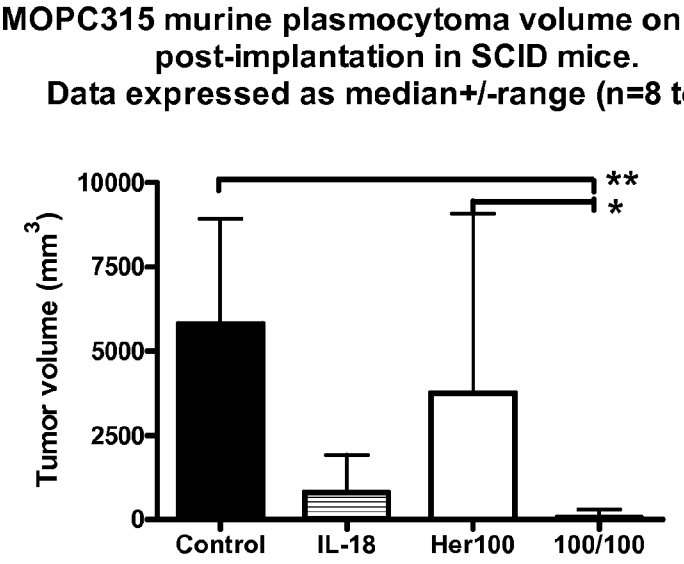

Effect of combination therapy with IL-18 and Herceptin
on the growth of MOPC315 murine plasmocytoma in SCID mice.
Data expressed as median+/-range (n=7 to 9).
Tumor volume (mm3)
12500
10000
7500
5000
2500
0
Therapy initiated
(day 7)
0
10
20
30
40
Day postimplantation
Control
Her100
Her50
Her25
IL-18
100/100
50/100
25/100

Figure 19



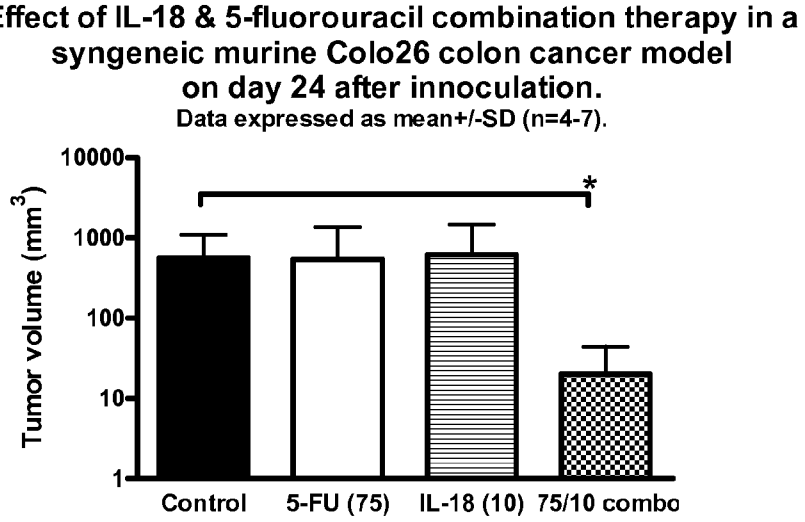
The IL-18 & Herceptin combinational therapy was significantly more effective than the monotherapy with Herceptin alone, or than the untreated control (*p<0.01, **p<0.001; Kruskal-Wallis analysis with Dunn's multiple comparison test).

Figure 20



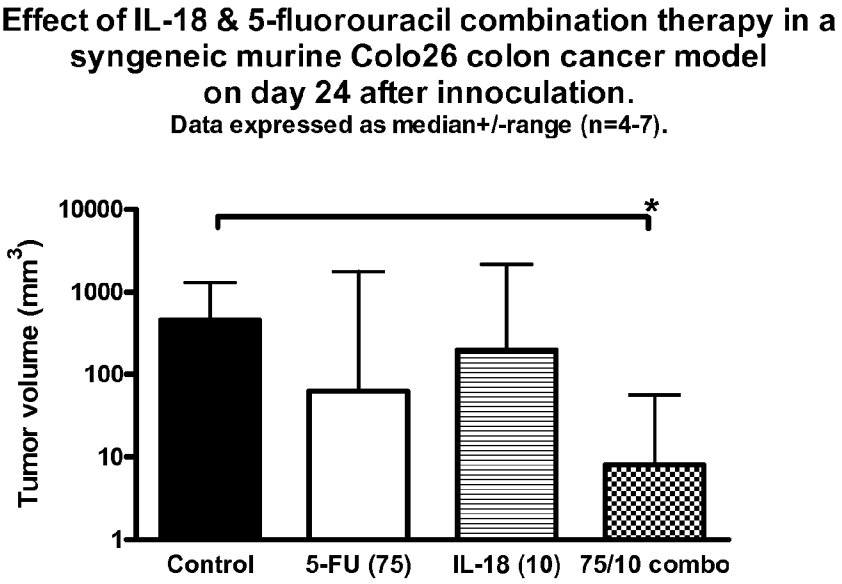
The IL-18 & Herceptin combinational therapy was significantly more effective than the monotherapy with Herceptin alone, or than the untreated control (*p<0.01, **p<0.001; Kruskal-Wallis analysis with Dunn's multiple comparison test).

Figure 21



The group treated with IL-18 & 5-fluorouracil combination therapy had significantly smaller tumors than the control group (*$p<0.05$) Kruskal-Wallis analysis with Dunn's multiple comparison test).

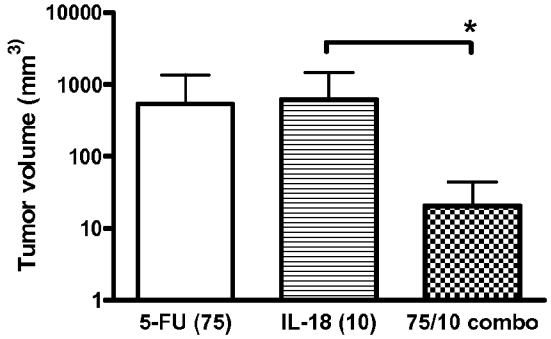
Figure 22



The group treated with IL-18 & 5-fluorouracil combination therapy had significantly smaller tumors than the control group (*p<0.05) Kruskal-Wallis analysis with Dunn's multiple comparison test).

Figure 23

Effect of IL-18 & 5-fluorouracil combination therapy in a syngeneic murine Colo26 colon cancer model on day 24 after innoculation.
Data expressed as mean+/-SD (n=6-7).



The group treated with IL-18 & 5-fluorouracil combination therapy had significantly smaller tumors than the IL-18 group (*p<0.05) Kruskal-Wallis analysis with Dunn's multiple comparison test).

Figure 24

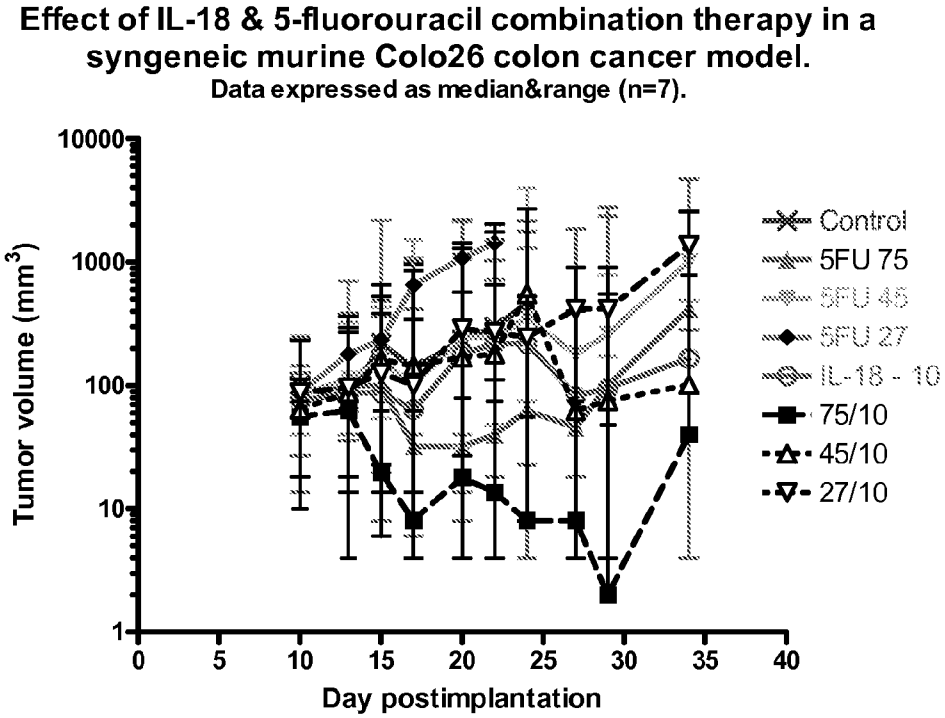

Effect of IL-18 & 5-fluorouracil combination therapy in a syngeneic murine Colo26 colon cancer model.
Data expressed as median&range (n=7).
Tumor volume (mm3)
10000
1000
100
10
1
0
5
10
15
20
25
30
35
40
Day postimplantation
Control
5FU 75
5FU 45
5FU 27
IL-18 - 10
75/10
45/10
27/10

Figure 25

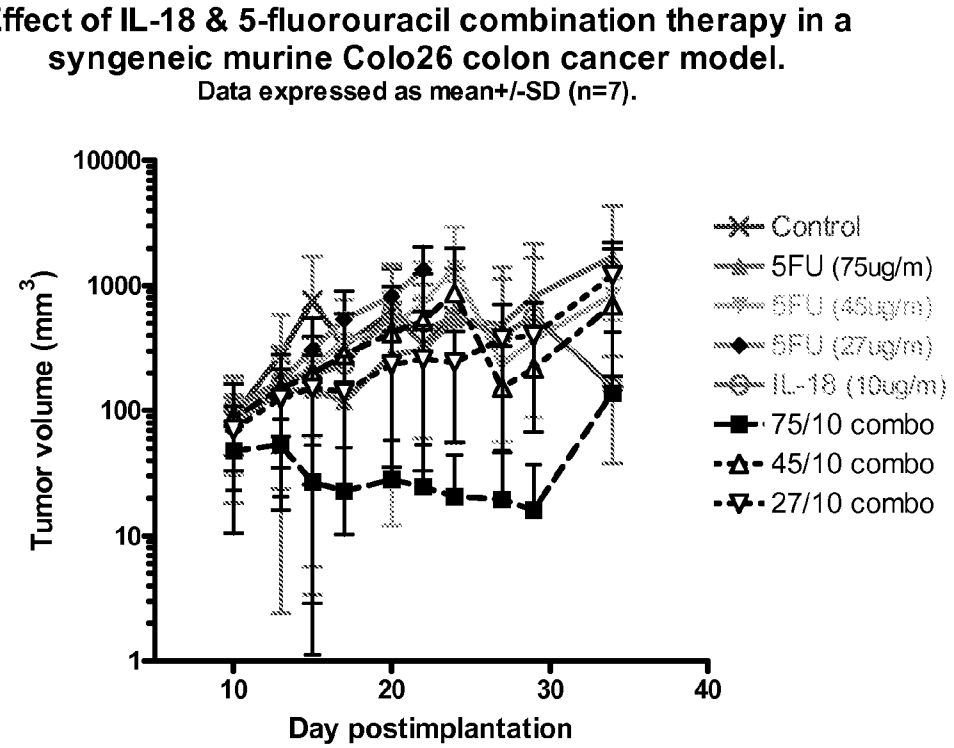
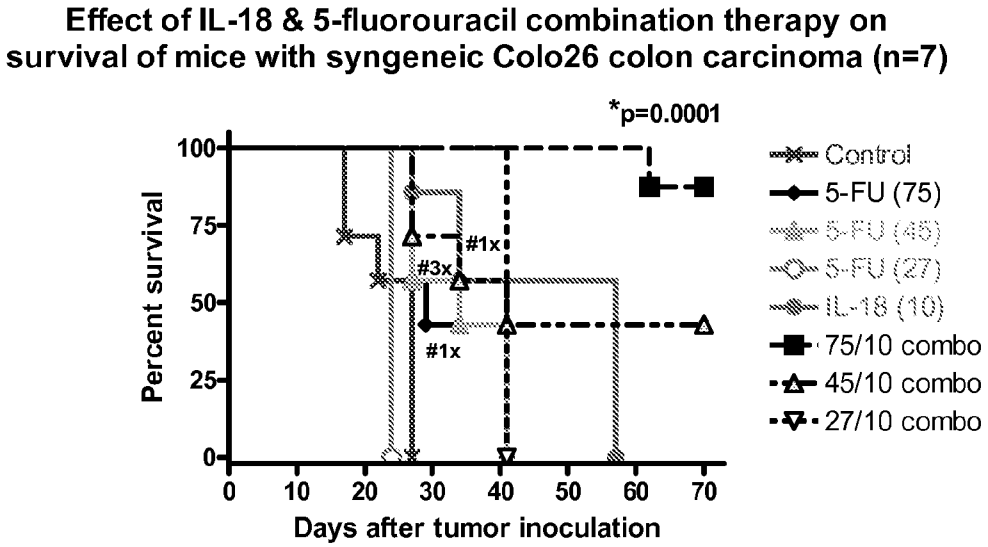
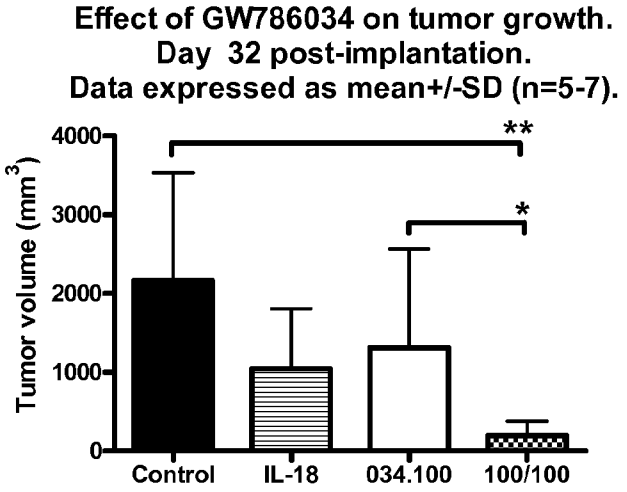

Effect of IL-18 & 5-fluorouracil combination therapy in a syngeneic murine Colo26 colon cancer model.
Data expressed as mean+/-SD (n=7).
Tumor volume (mm3)
10000
1000
100
10
1
10
20
30
40
Day postimplantation
Control
5FU (75ug/m)
5FU (45ug/m)
5FU (27ug/m)
IL-18 (10ug/m)
75/10 combo
45/10 combo
27/10 combo

Figure 26



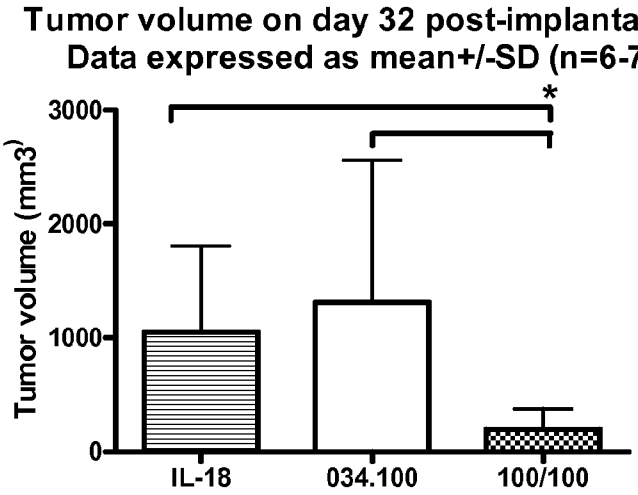
*Kaplan-Meyer survival curve comparison with Logrank test determined statistical difference between the treatment groups ($p<0.0001$).
Marked number indicates number of deaths due to toxicity. Note: all other deaths were tumor growth related (euthanized for ethical reasons when tumor volume reached predetermined size, or spontaneous cancer death).

Figure 27



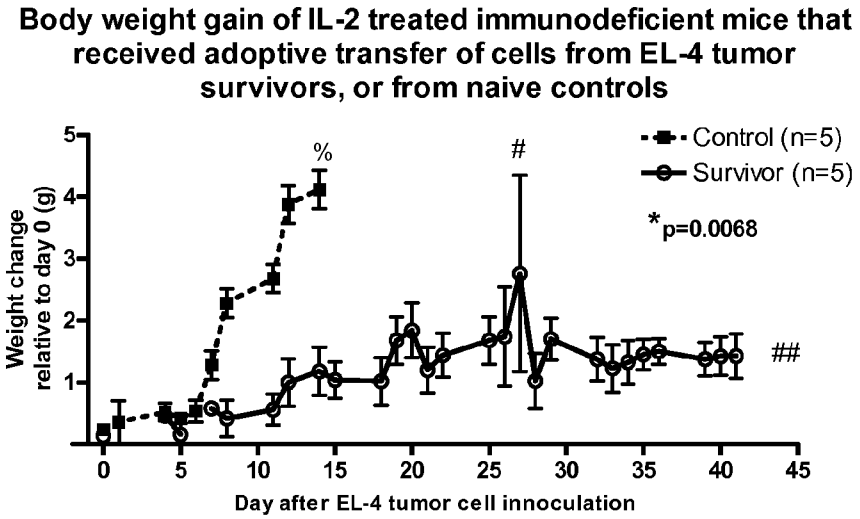
Statistically significant difference was determined in the group treated with the IL-18 & GW786034 combination therapy as compared to the untreated control group ($p<0.01$), and as compared to the monotherapy with GW786034 ($p<0.05$) (Kruskal-Wallis analysis with Dunn's multiple comparison test).

Figure 28



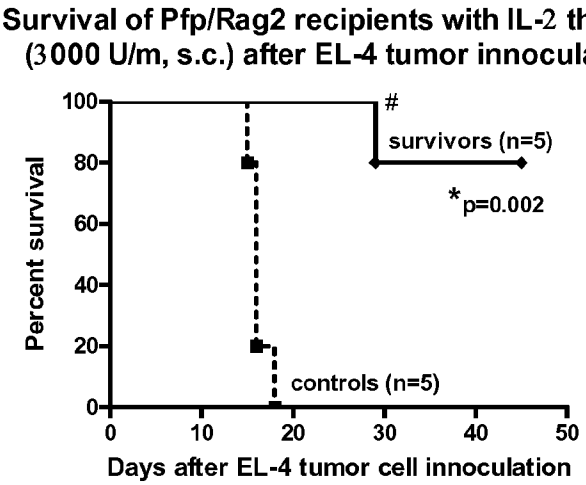
Statistically significant difference was determined in the group treated with the IL-18 & GW786034 combination therapy as compared to the monotherapy with GW786034, or IL-18 alone ((p<0.05; Kruskal-Wallis analysis with Dunn's multiple comparison test).

Figure 29



% All control mice died due of tumor related death within 2 weeks.
# One mouse euthanized due to large tumor mass and ascites.
All survivors tumor free except one with small palpable abdominal mass.
* Statistically significant difference (paired t-test).

Figure 30



One survivor mouse was euthanized due to extensive tumor mass and ascites.

* Statistically significant difference (Kaplan-Meyer's survival curve with Logrank test)