Bacteria Cancer Therapy

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The founder of cancer immunotherapy

Coley WB

Historical background

Coley WB. Contribution to the knowledge of sarcoma. *Ann Surgery* 1890;**14:**199–220.

Coley WB. Late results of the treatment of inoperable sarcoma by the mixed toxins of erysipelas and *Bacillus prodigiosus*. *Am J Med Sci.* 1906;**131:**375–430.

Nauts HC, Swift WE, Coley BL. The treatment of malignant tumors by bacterial toxins as developed by the late William B Coley, MD, reviewed in the light of modern research. *Cancer Res.* 1946;**6:**205–16.

Nauts HC, Fowler GAA, Bogatko FH. A review of the influence of bacterial infection and of bacterial products (Coley's toxins) on malignant tumors in man. *Acta Medica Scandinavica.* 1953;**145**(suppl 276)**:**1–105.

Carswell EA, Old LJ, Kassel RL, et al. An endotoxin induced serum factor that causes necrosis of tumors. *Proc Natl Acad Sci USA.* 1975;**72:**3666–70.

Historical background

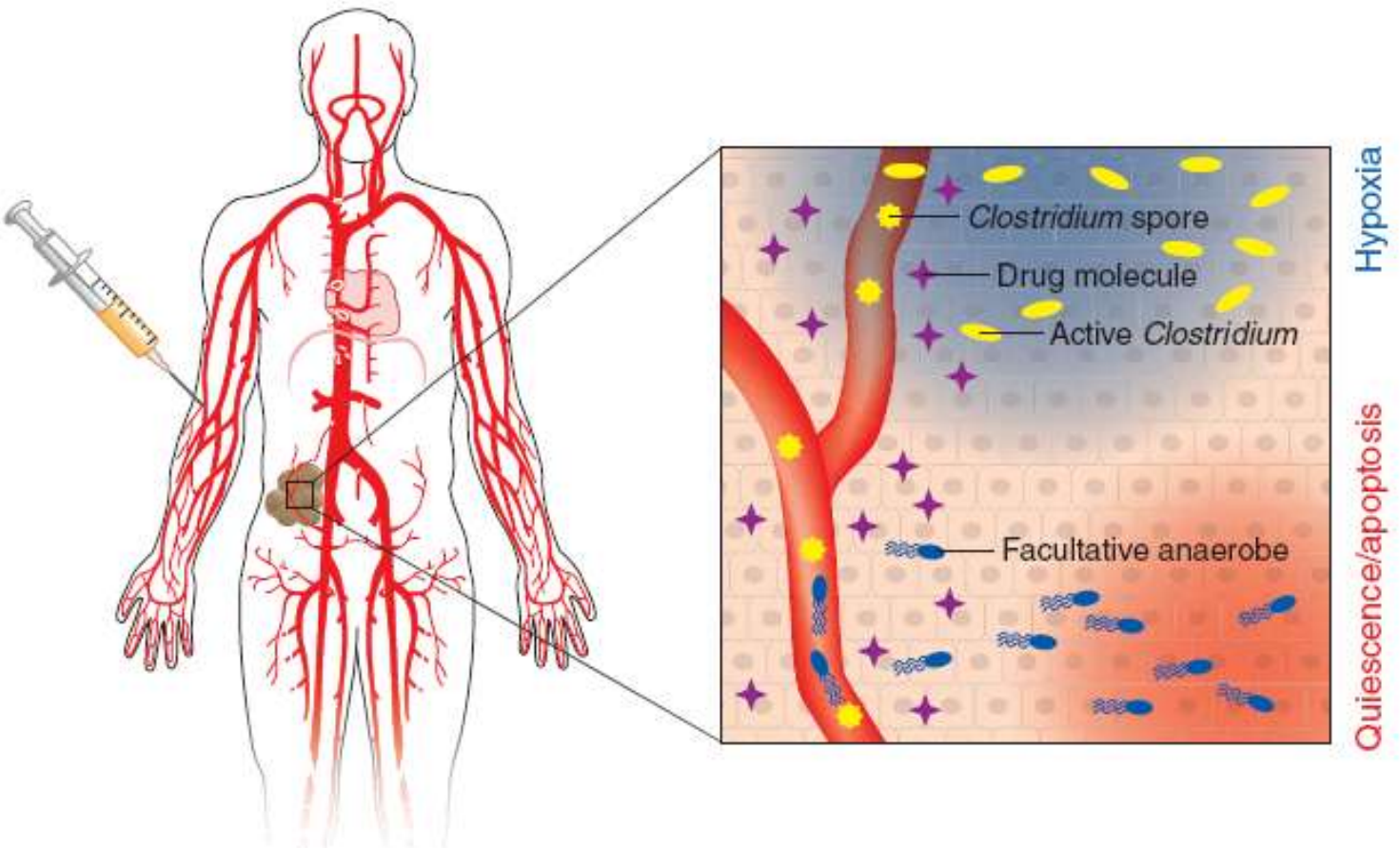
Engelbart K, Gericke D. Oncolysis by clostridia. V. transplanted tumors of the hamster. *Cancer Res*. 1964; **24:** 234-38.

Möse JR, Möse G, Propst A, Heppner F. Oncolysis of malignant tumors by *Clostridium* strain M 55. *Med Klin.* 1967;**62:**189-93.

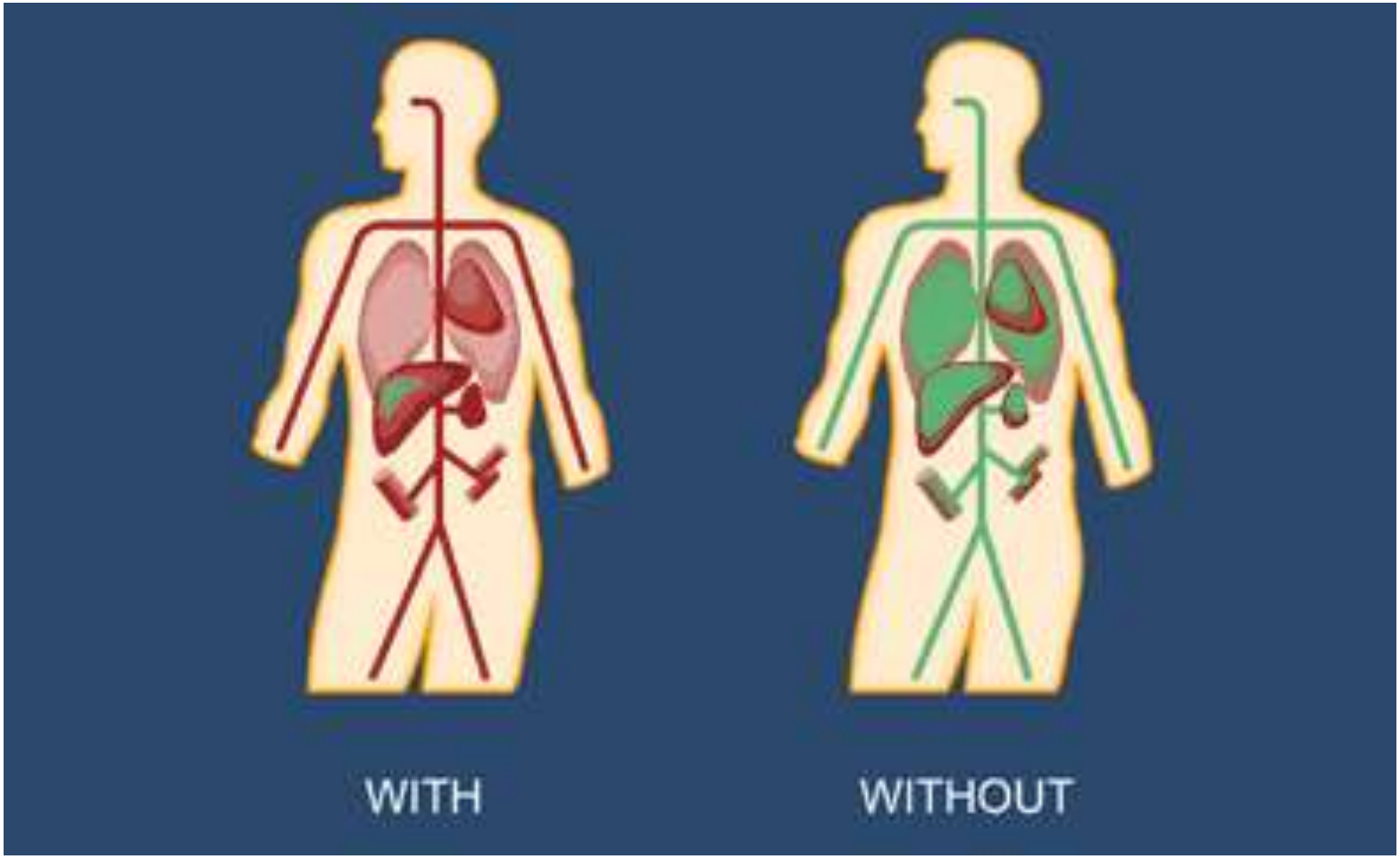
Kohwi Y, Imai K, Tamura Z, Hashimoto Y. Antitumor effect of Bifidobacterium infantis in mice. *Gann.* 1978;**69**:613-8.

Kimura NT, Taniguchi S, Aoki K, Baba T. Selective localization and growth of *Bifidobacterium bifidum* in mouse tumors following intravenous administration. *Cancer Res*. 1980;**40:**2061-8.

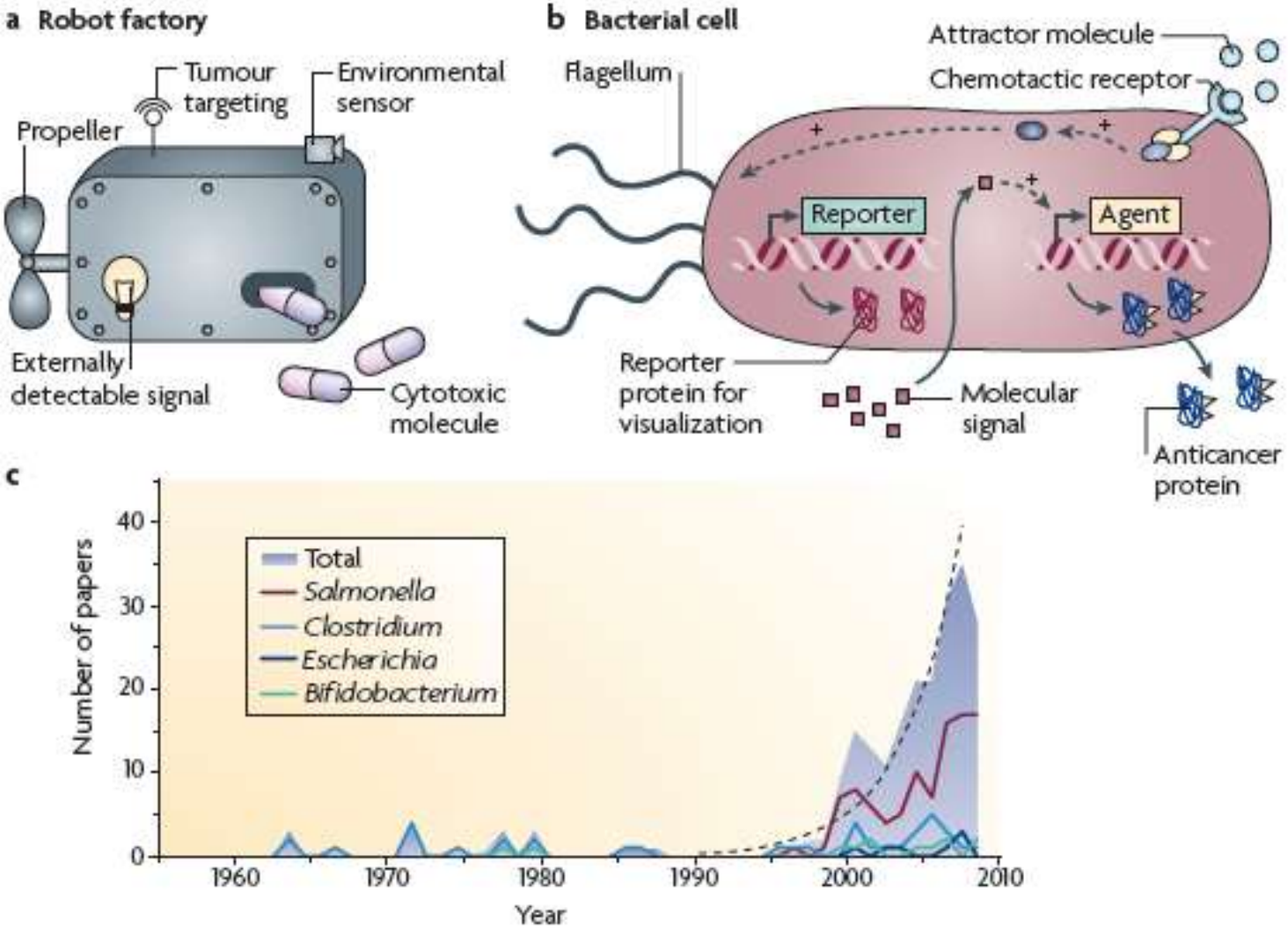
Targeting of obligate and facultative anaerobes to tumors



Targeting vectors and systemic delivery



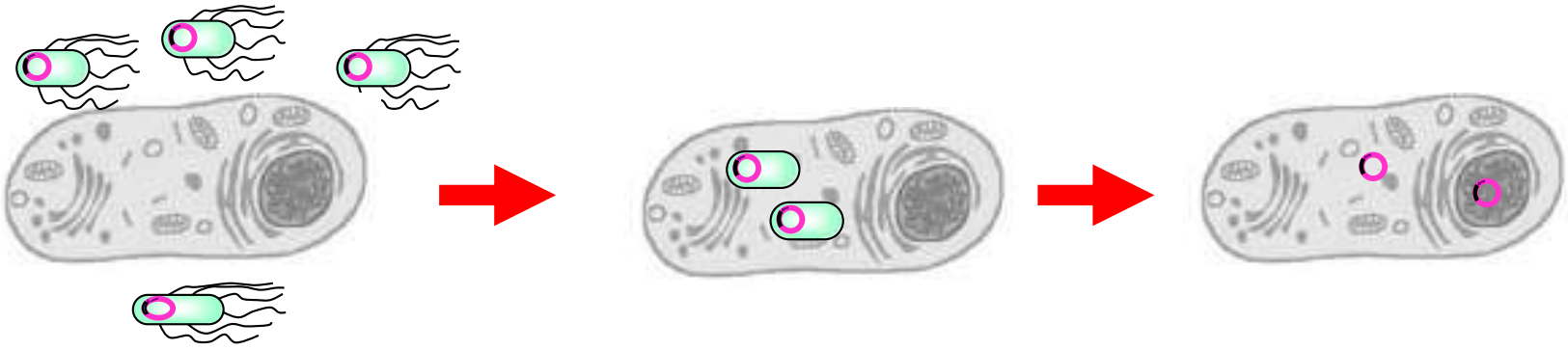
Bacteria are the optimal robot factory cancer therapy



Nature Rev. Cancer 10: 785, 2010.

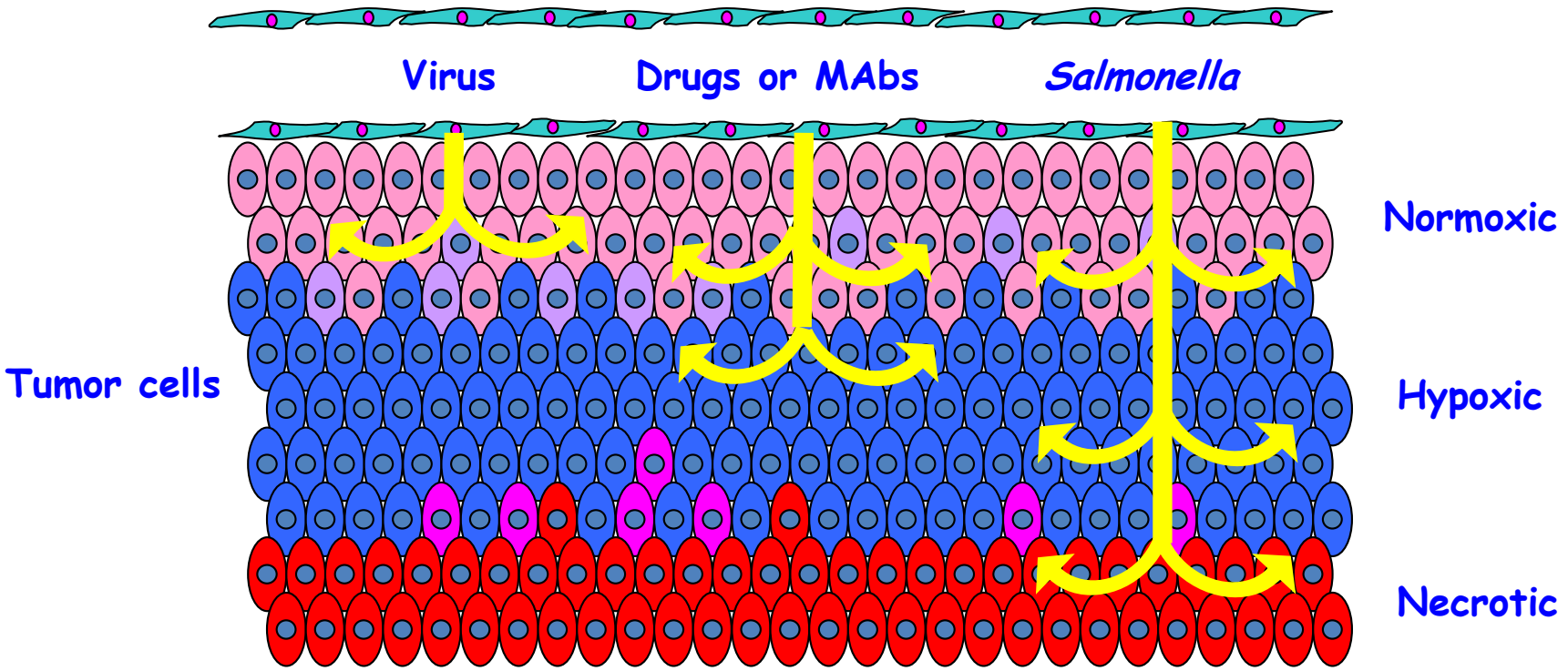
Bactofection versus alternative gene therapy

	Viral vectors	*Nonviral vectors*	*Bacterial vectors*
Safety	+	+++	+
Efficiency	+++	+	+
Low production costs	+	++	+++
Simple production	+	++	+++
Simple delivery	++	+	+++
Amount of delivered DNA	++	+	+++



Gene Ther. 13: 101, 2006.

Salmonella may bring new approach to cancer therapy



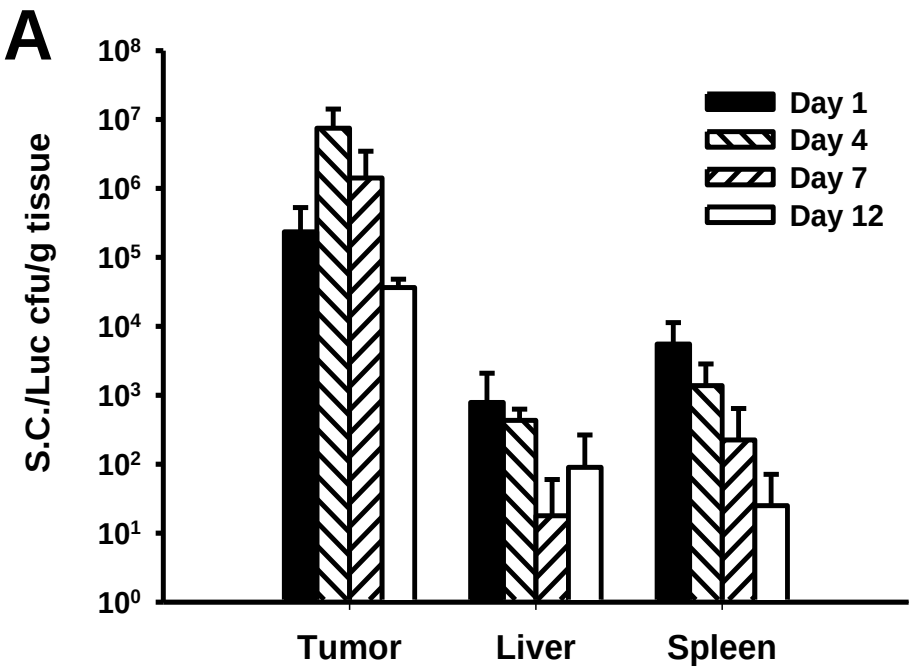
Advantages of *Salmonella*:

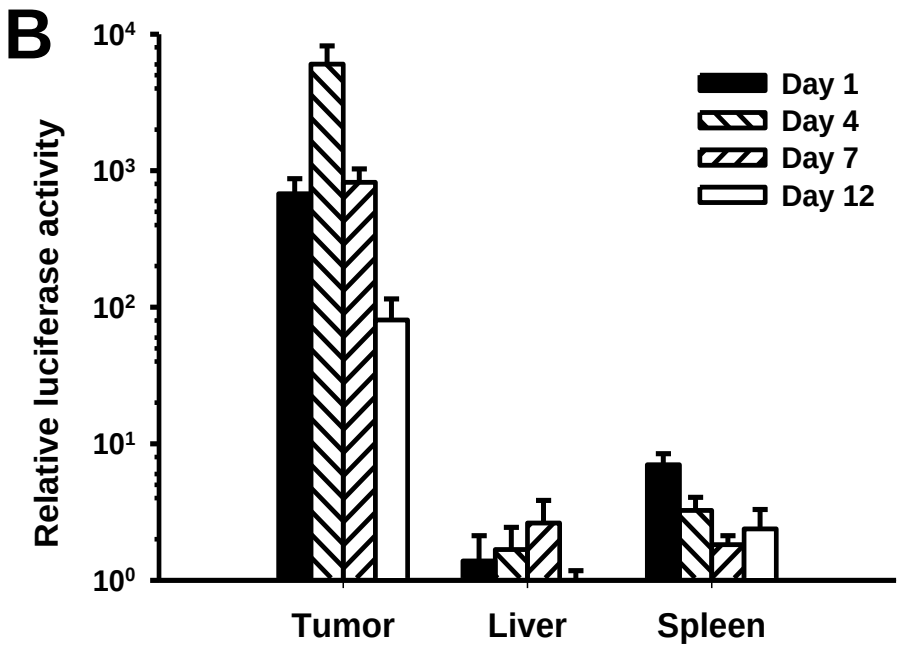
- Motility
- Transgene capacity
- Facultative anaerobic
- Cheaper

Appl. Microbiol. Biotechnol. 93: 517, 2012.

Employment of *Salmonella* in cancer gene therapy

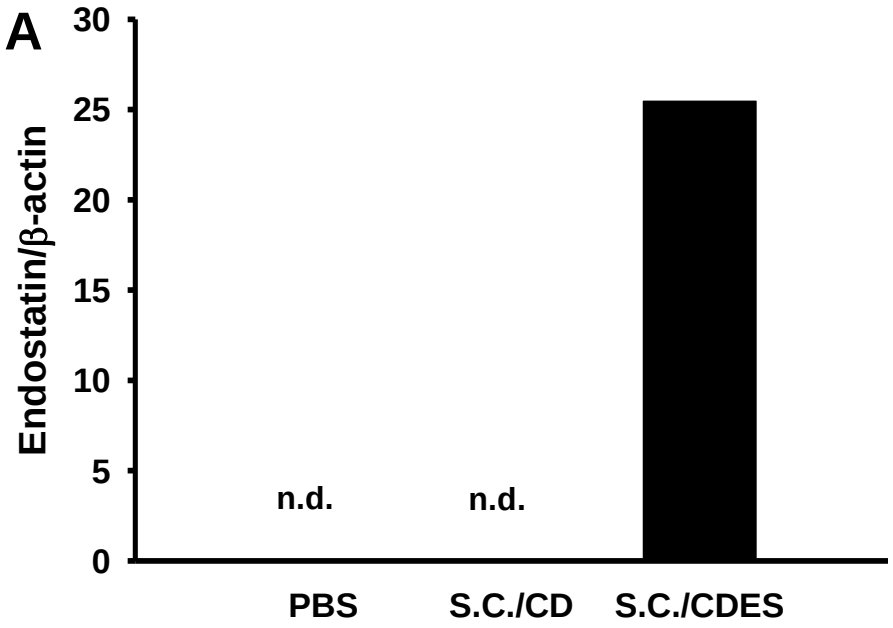
Plasmid DNA transfer from *Salmonella* to tumor *in vivo*





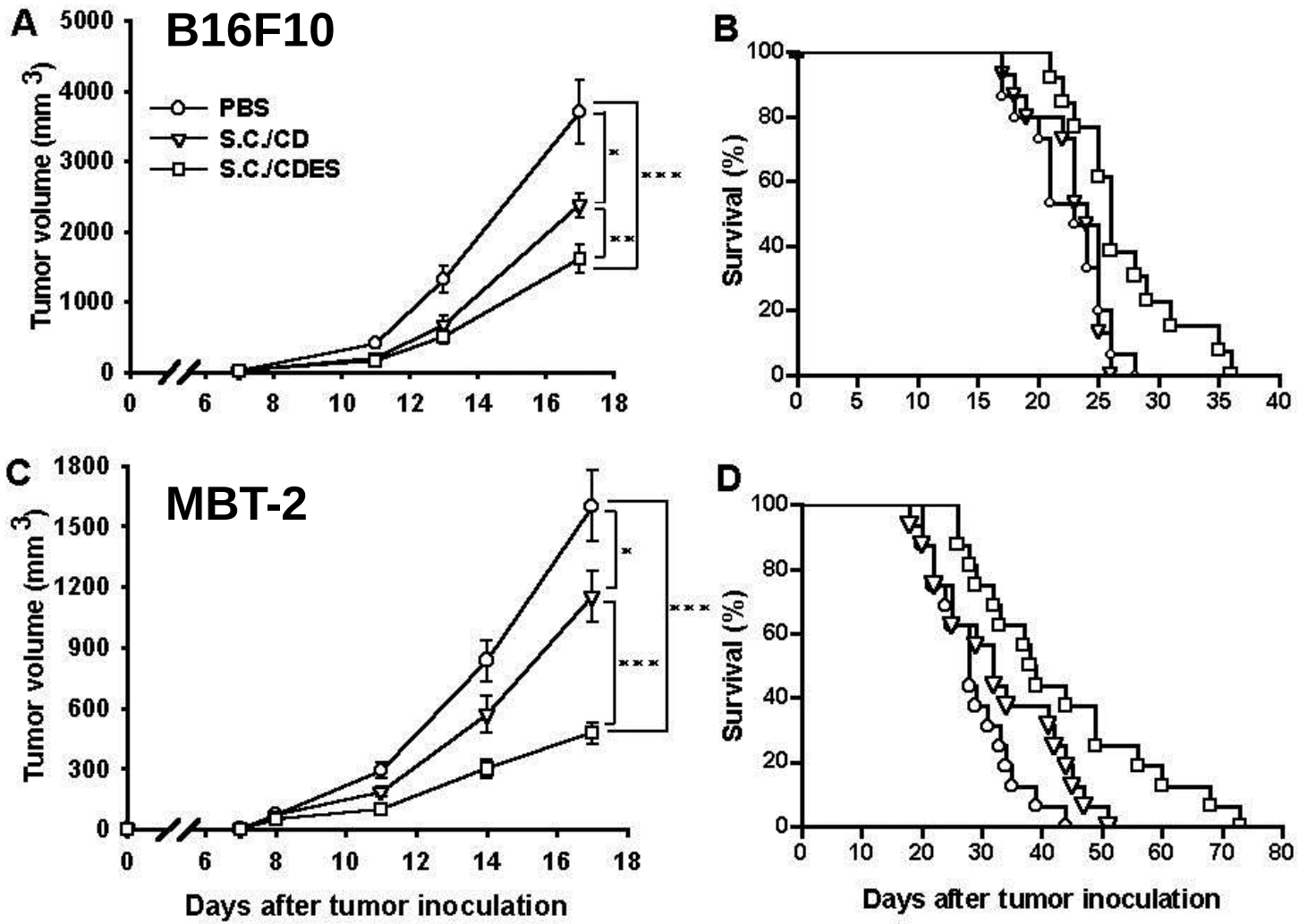
Salmonella **preferentially accumulated and retained in large amounts in the tumors where salmonella-mediated gene transfer occurred.**

Expression of angiogenic inhibitors in cells via *Salmonella*-mediated gene transfer



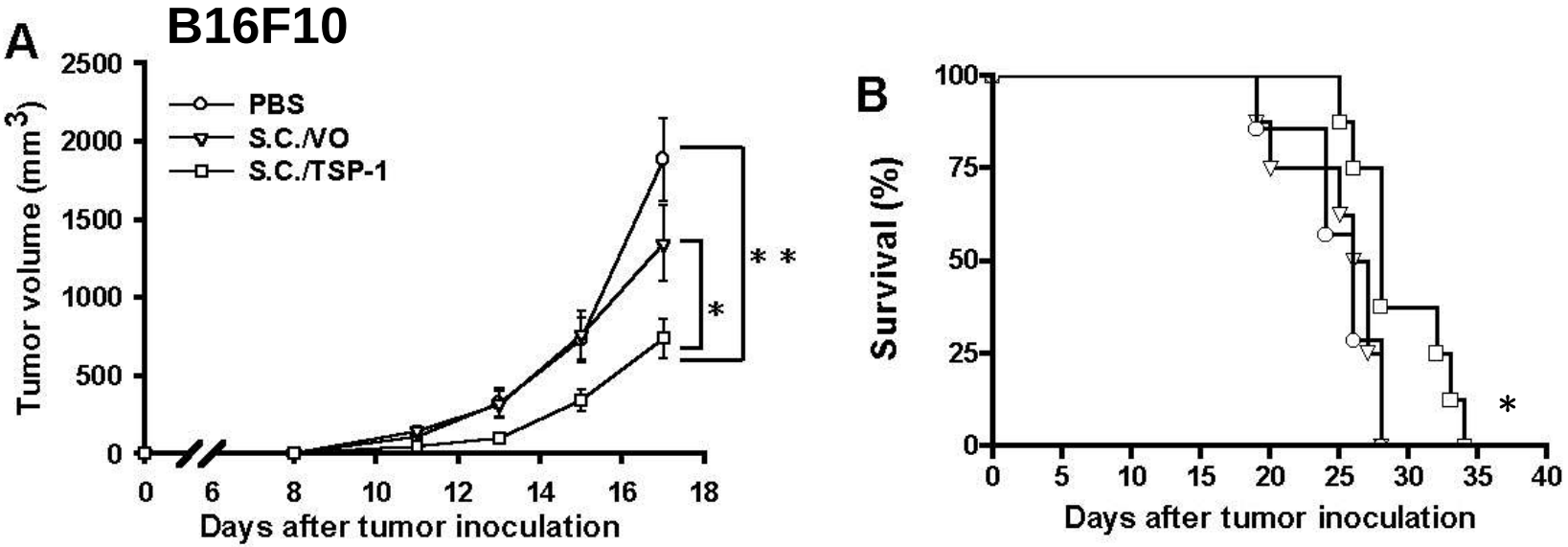
Cancer Gene Ther. 12: 175, 2005.

Antitumor effects of *Salmonella* carrying endostatin gene on tumor-bearing mice



J. Gene. Med. 6: 1382, 2004.

Antitumor effects of *Salmonella* carrying TSP-1 gene on mice bearing subcutaneous melanoma

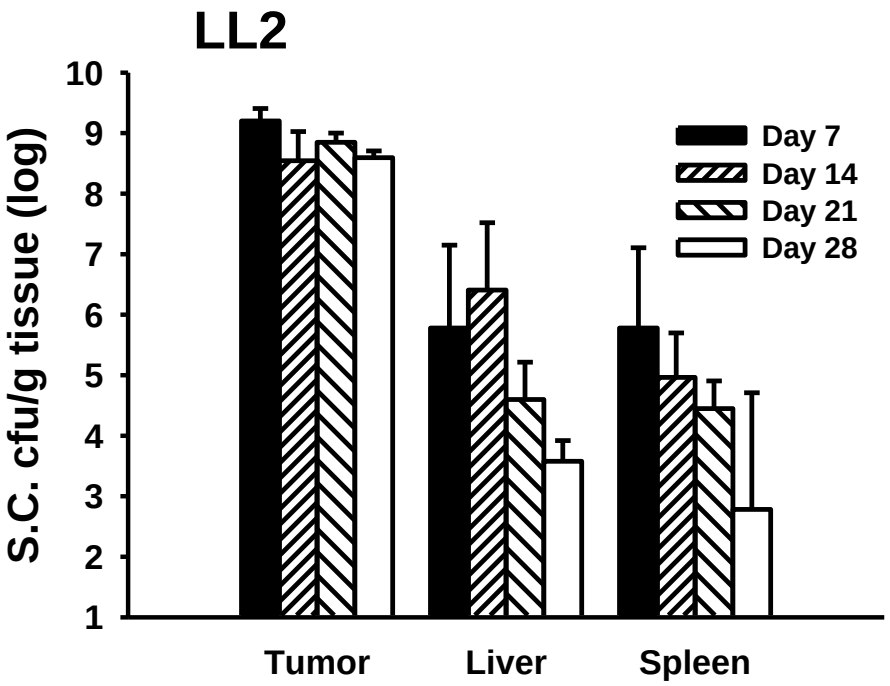


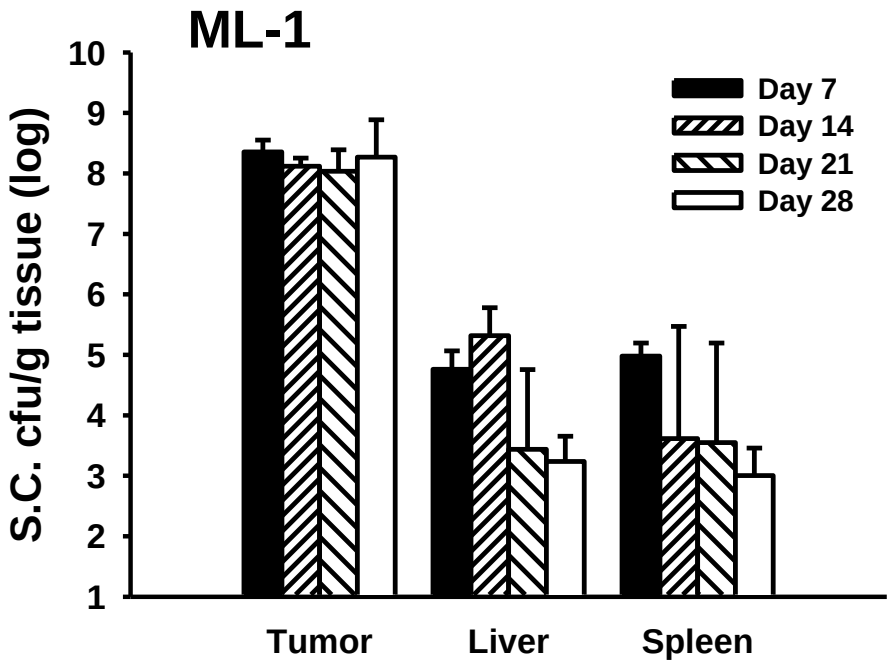
Cancer Gene Ther. 12: 175, 2005.

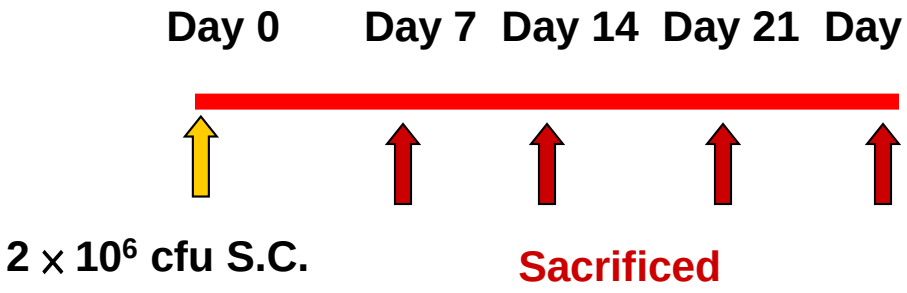
Salmonella **carrying a eukaryotic expression vector encoding antiangiogenic genes exerted antitumor effects on various tumor models.**

Systemic administration of attenuated *Salmonella* in combination with cisplatin for cancer therapy

Tumor-targeting potential of *Salmonella* in immunocompetent mice

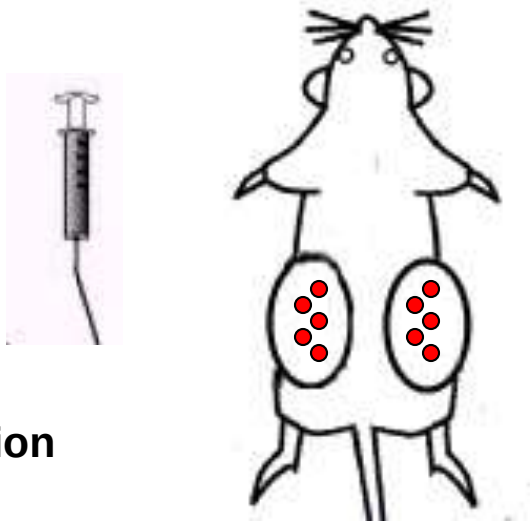




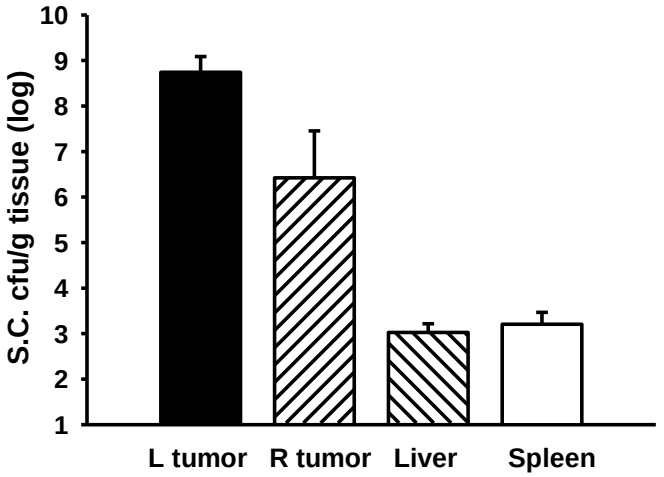


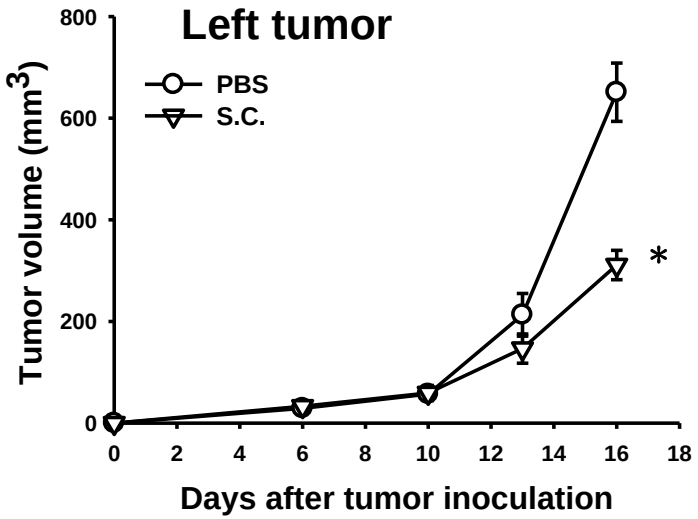
Mol. Ther. 11: 707, 2005.

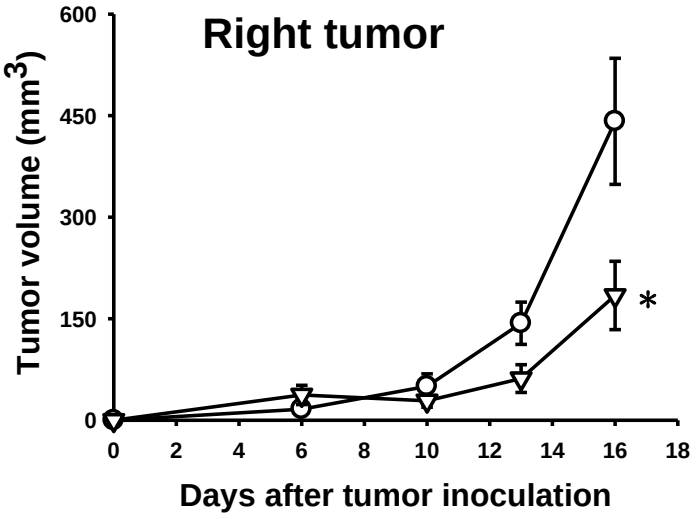
Preferential accumulation of *Salmonella* in the bilateral tumors from mice administered locally with *Salmonella*



i.t. injection

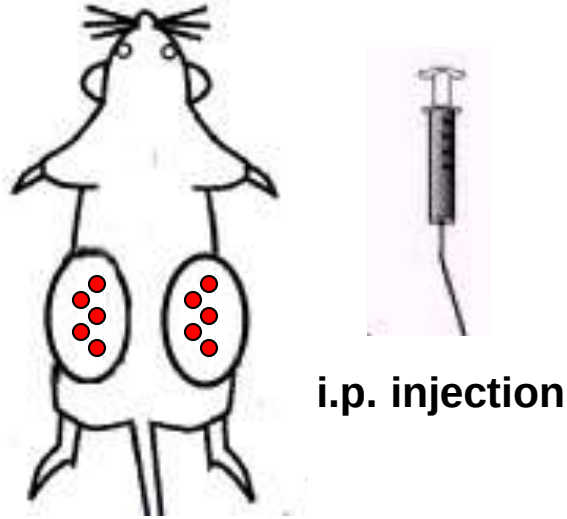




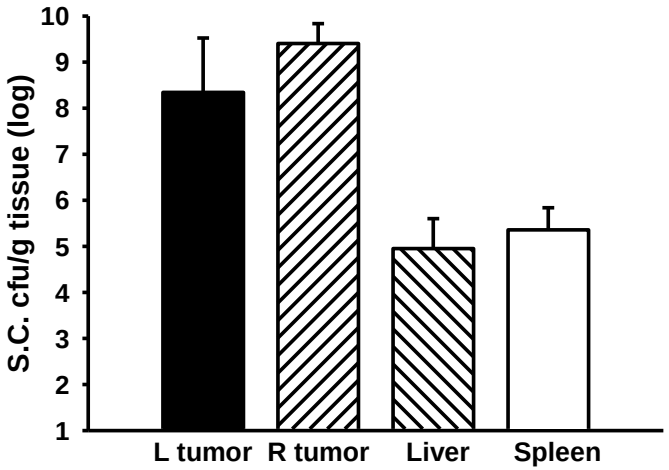


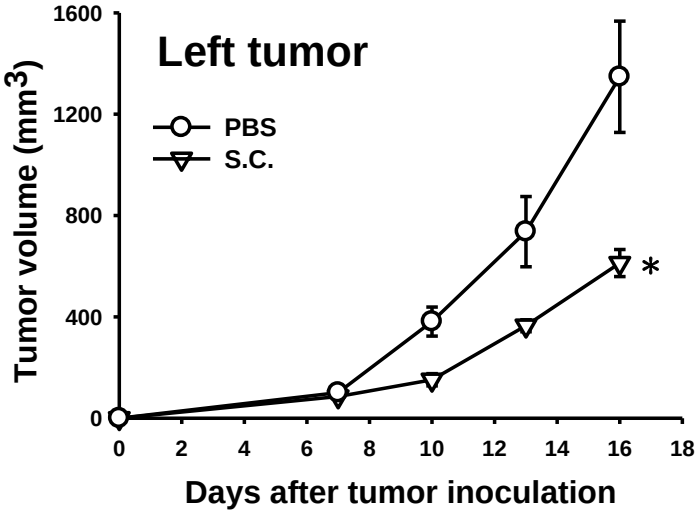
Mol. Ther. 11: 707, 2005.

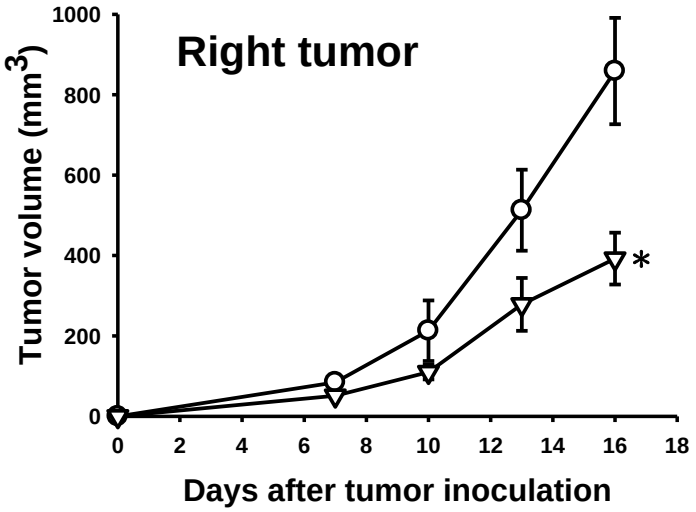
Preferential accumulation of *Salmonella* in the bilateral tumors from mice administered systematically with *Salmonella*



i.p. injection



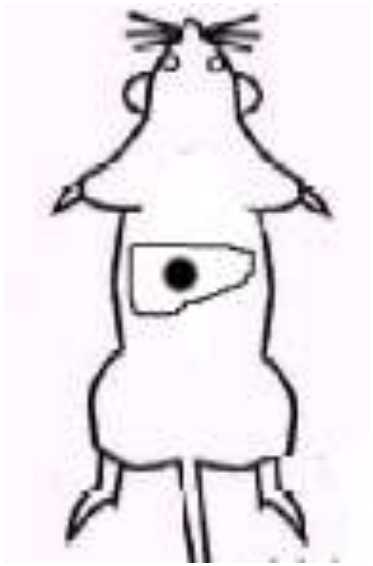




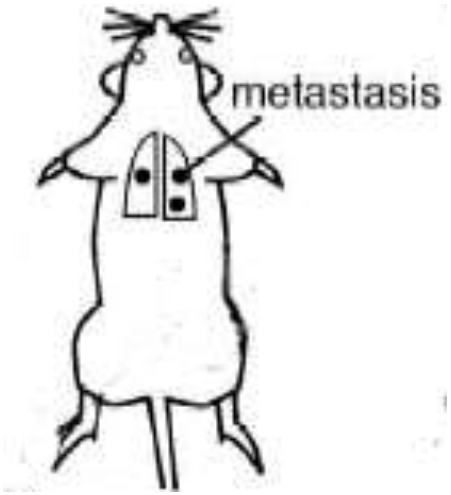
The tumor-targeting property of *Salmonella* provides impetus to explore its use in inhibiting tumor growth at distant sites.

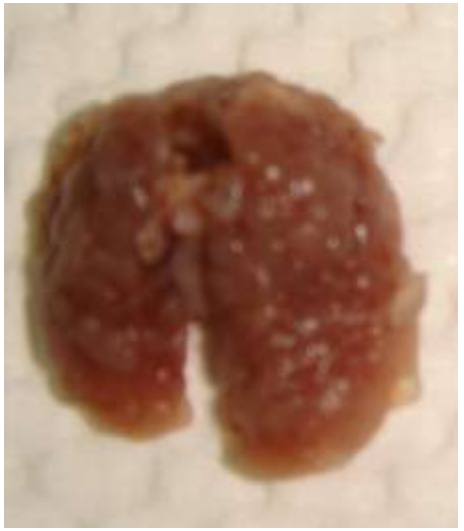
Establishment of orthotopic tumor models

Orthotopic liver tumor model



Orthotopic lung tumor model

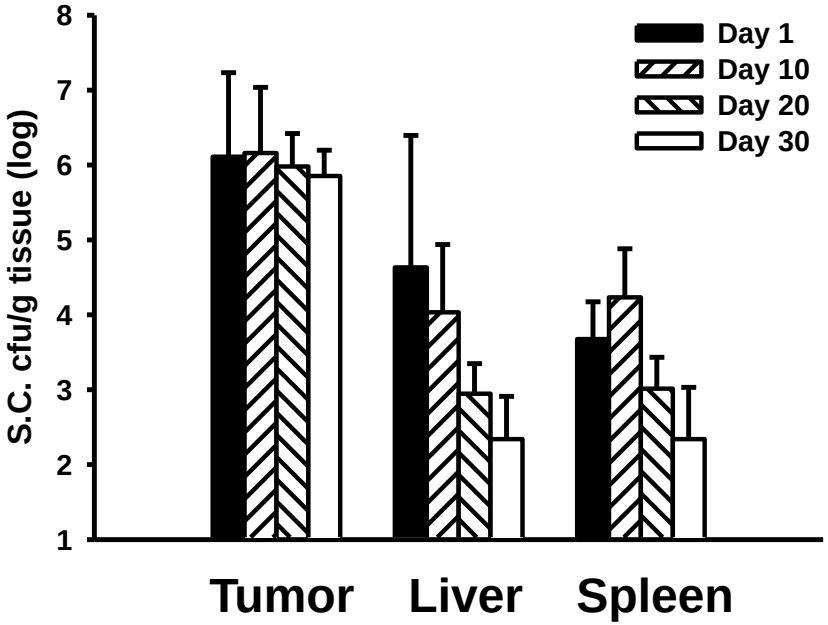


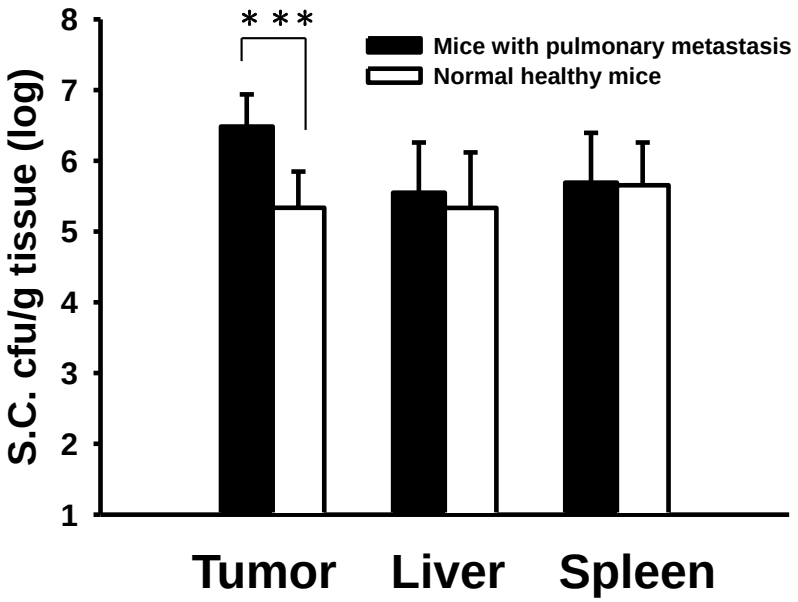


Mol. Ther. 11: 707, 2005.

Int. J. Cancer 122:930, 2008.

Preferential accumulation of *Salmonella* in orthotopic tumors



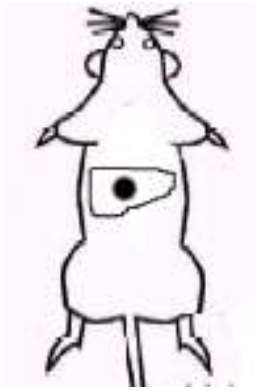


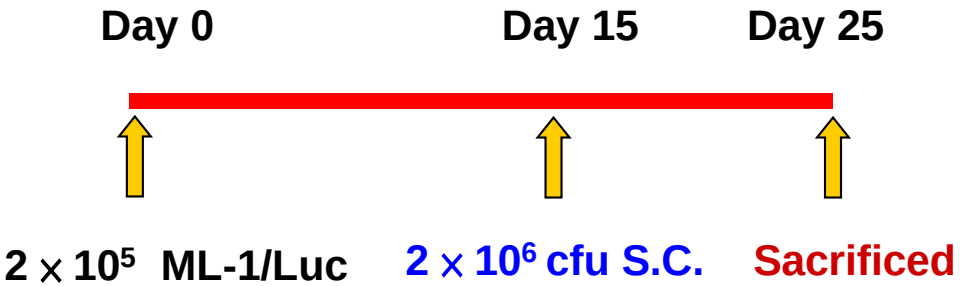
Mol. Ther. 11: 707, 2005.

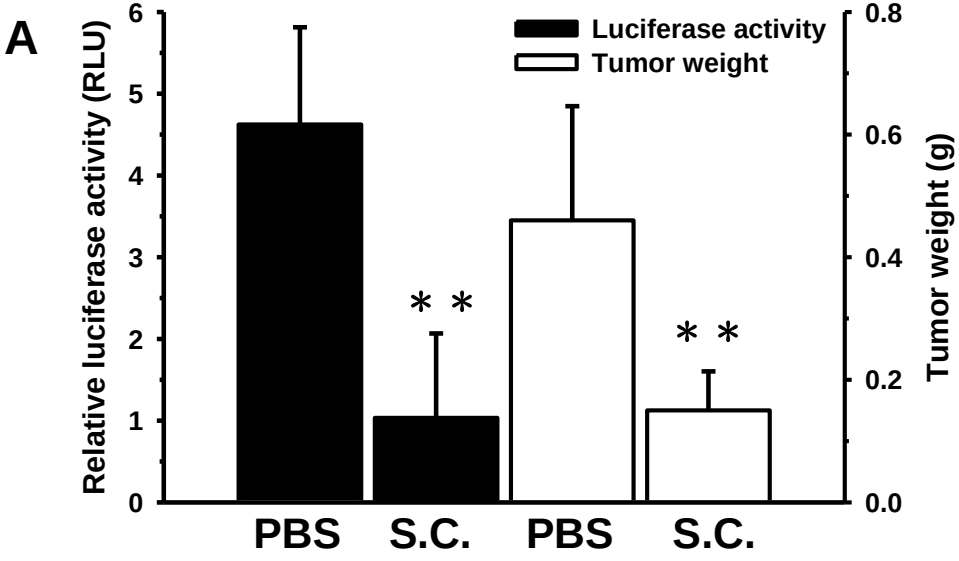
Int. J. Cancer 122:930, 2008.

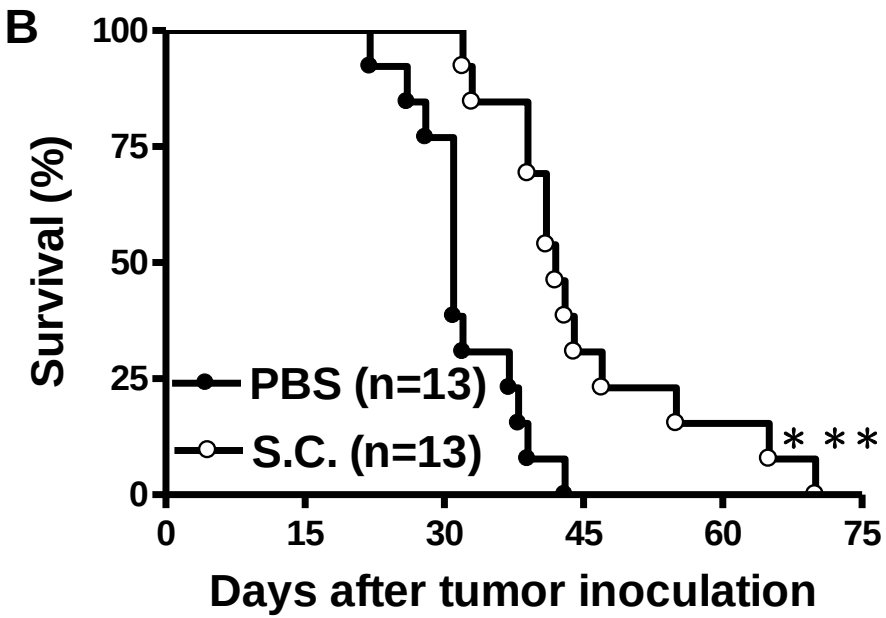
Salmonella **accumulated in not only subcutaneous but also orthotopic tumors after systemic administration.**

Antitumor effects of *Salmonella* on orthotopic ML-1 tumors



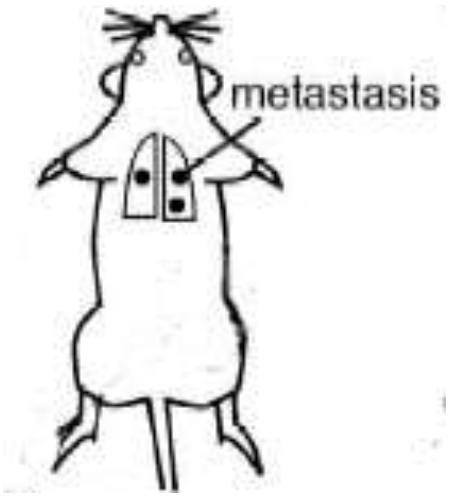


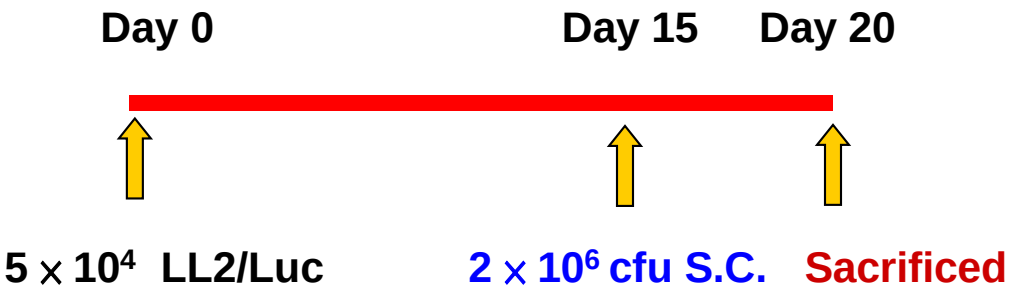


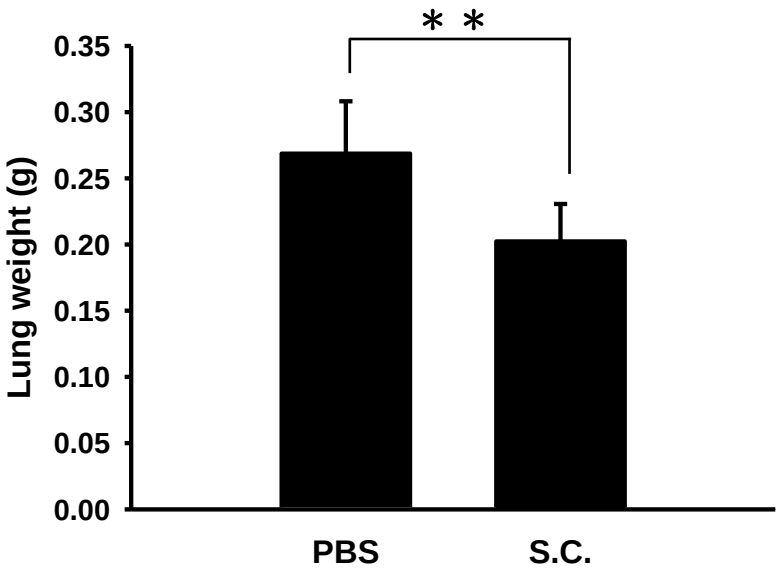


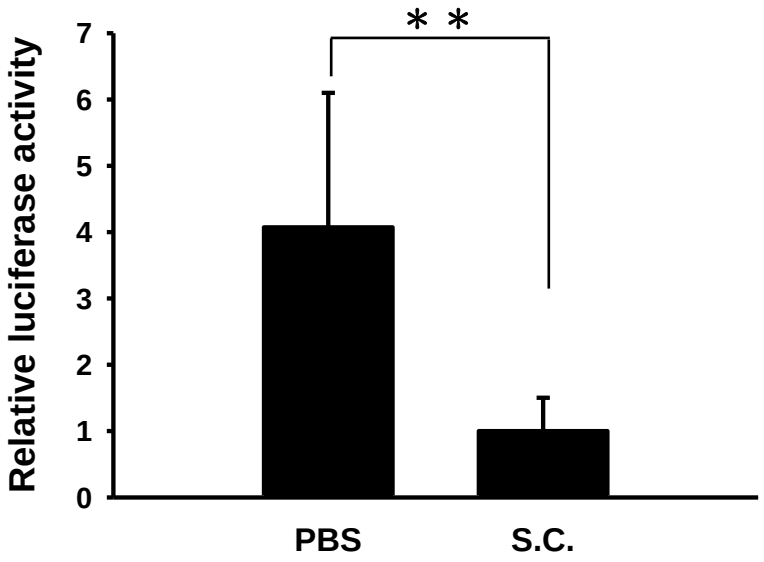
Int. J. Cancer 122:930, 2008.

Antitumor effects of *Salmonella* on mice bearing pulmonary metastatic tumors



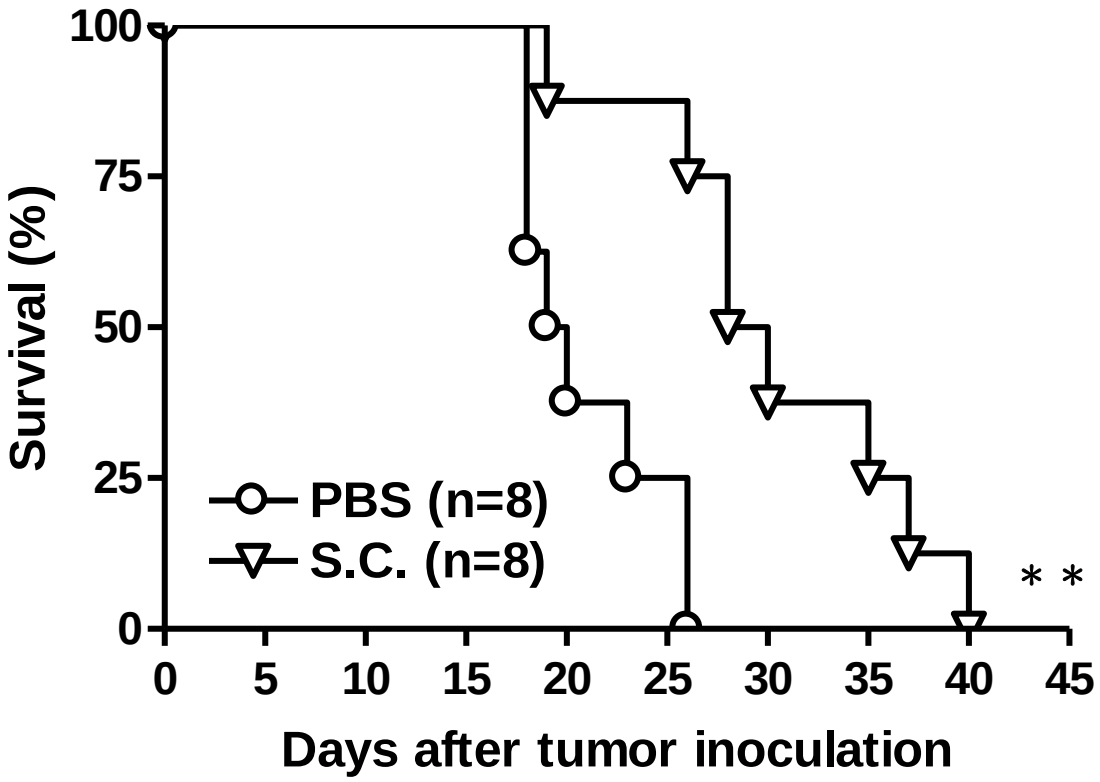






Mol. Ther. 11: 707, 2005.

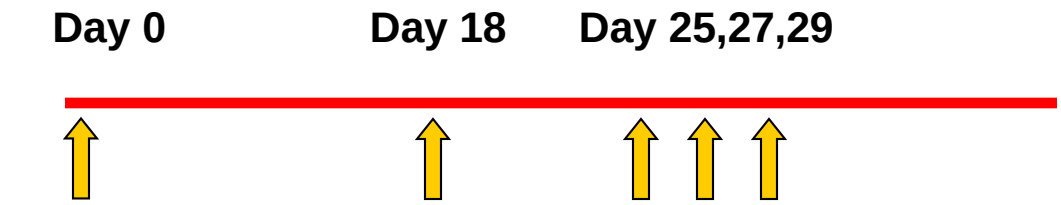
Prolongation in survival time of the mice bearing experimental metastasis by systemic delivery of *Salmonella*

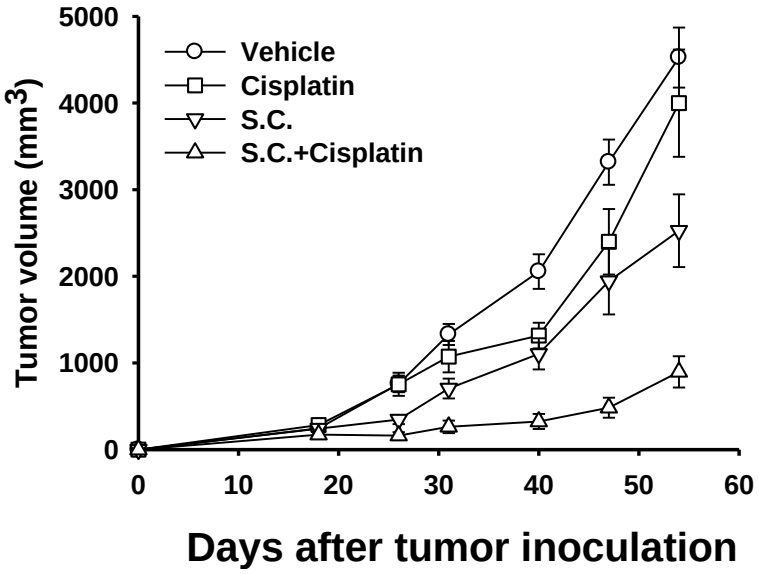


Mol. Ther. 11: 707, 2005.

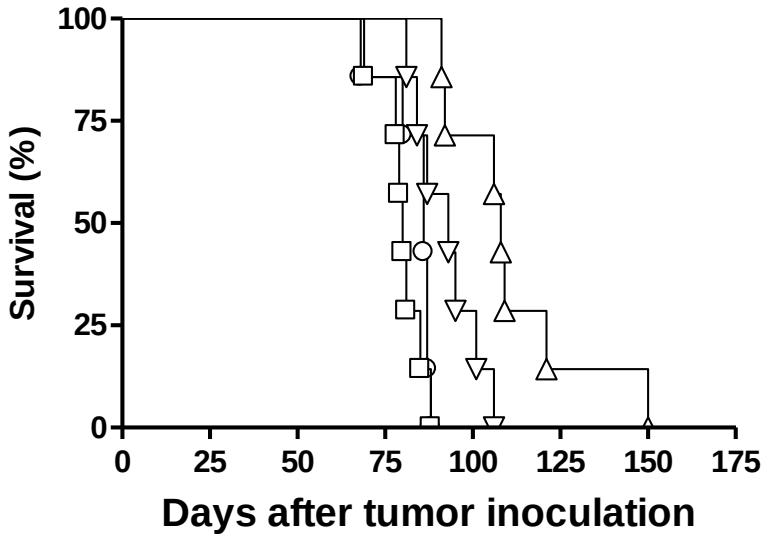
Systemic delivery of *Salmonella* delayed tumor growth and enhanced survival of the mice bearing orthotopic tumors.

Additive antitumor effects of *Salmonella* in combination with cisplatin on subcutaneous ML-1 tumors





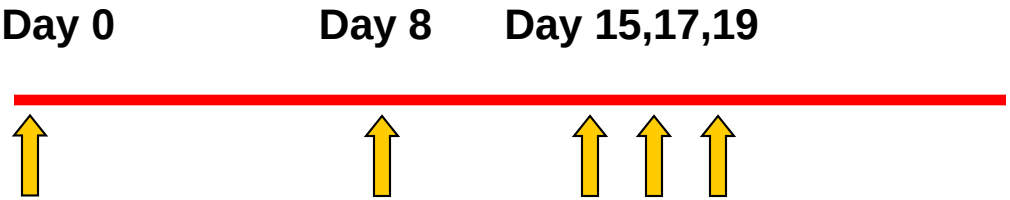
(*P* < 0.001 for S.C.+cisplatin *versus* cisplatin or vehicle; *P*<0.01 for S.C.+cisplatin *versus* S.C. and for S.C. *versus* vehicle)



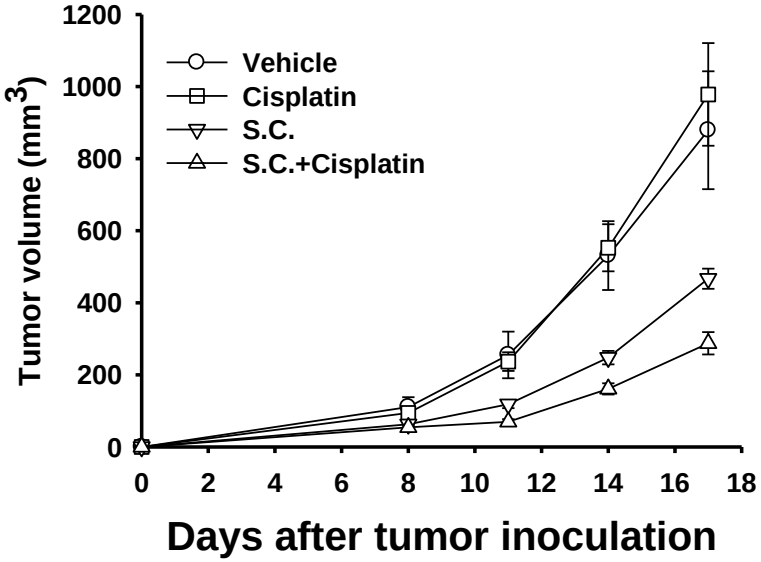
(*P* < 0.001 for S.C.+cisplatin *versus* cisplatin or vehicle; *P*<0.05 for S.C.+cisplatin *versus* S.C. and for S.C. *versus* vehicle)

Mol. Ther. 11: 707, 2005.

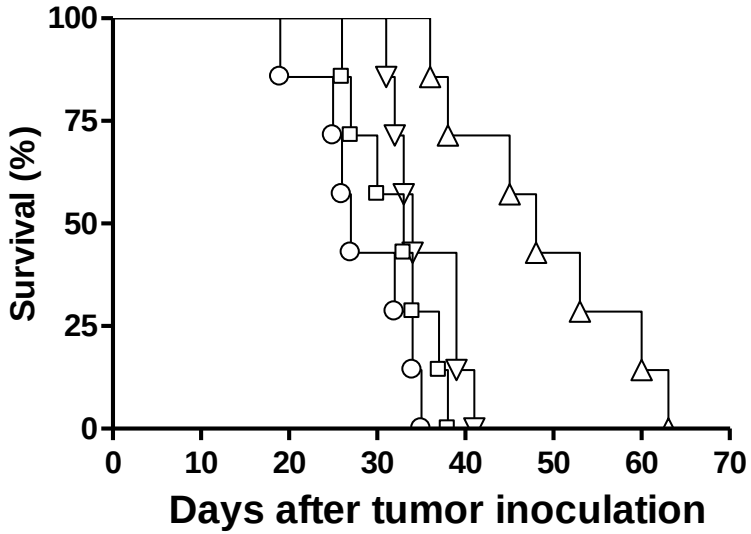
Additive antitumor effects of *Salmonella* in combination with cisplatin on subcutaneous LL2 tumors



1×10^6 LL2 2×10^6 cfu S.C. cisplatin 2mg/kg



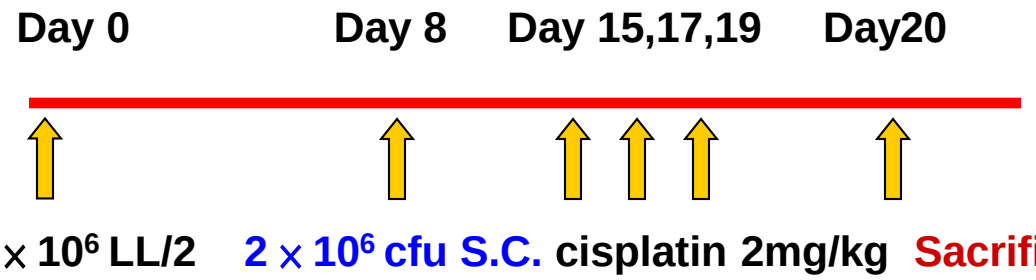
(P<0.001 for S.C.+cisplatin *versus* cisplatin; $P < 0.01$ for S.C.+cisplatin *versus* S.C. or vehicle; $P < 0.05$ for S.C. *versus* vehicle)

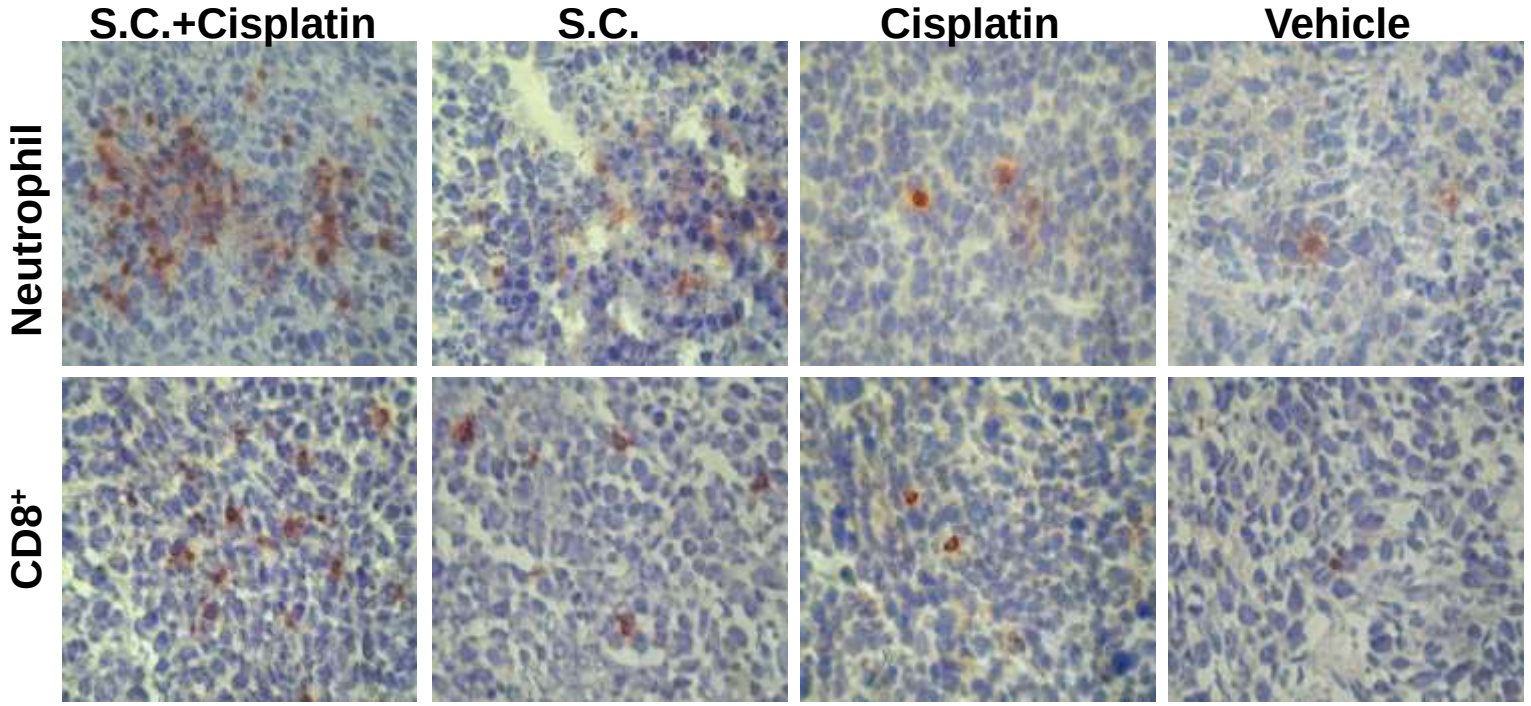


($P < 0.01$ for S.C.+cisplatin *versus* S.C., cisplatin, or vehicle; P<0.05 for S.C. *versus* vehicle)

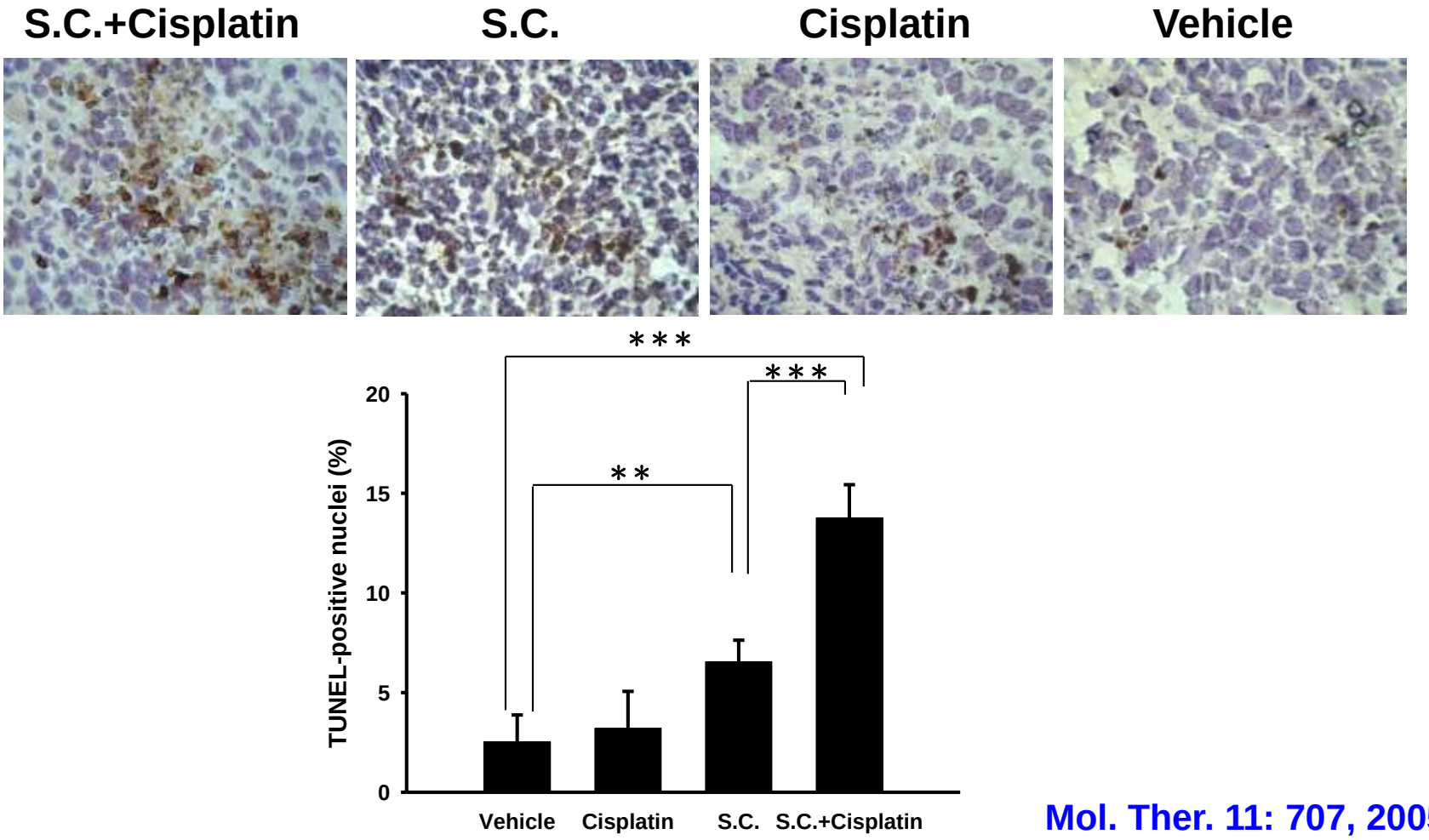
Mol. Ther. 11: 707, 2005.

Increases in neutrophil and CD8$^+$ T-cell infiltrates in the tumors from LL2 tumor-bearing mice treated with *Salmonella* in combination with cisplatin





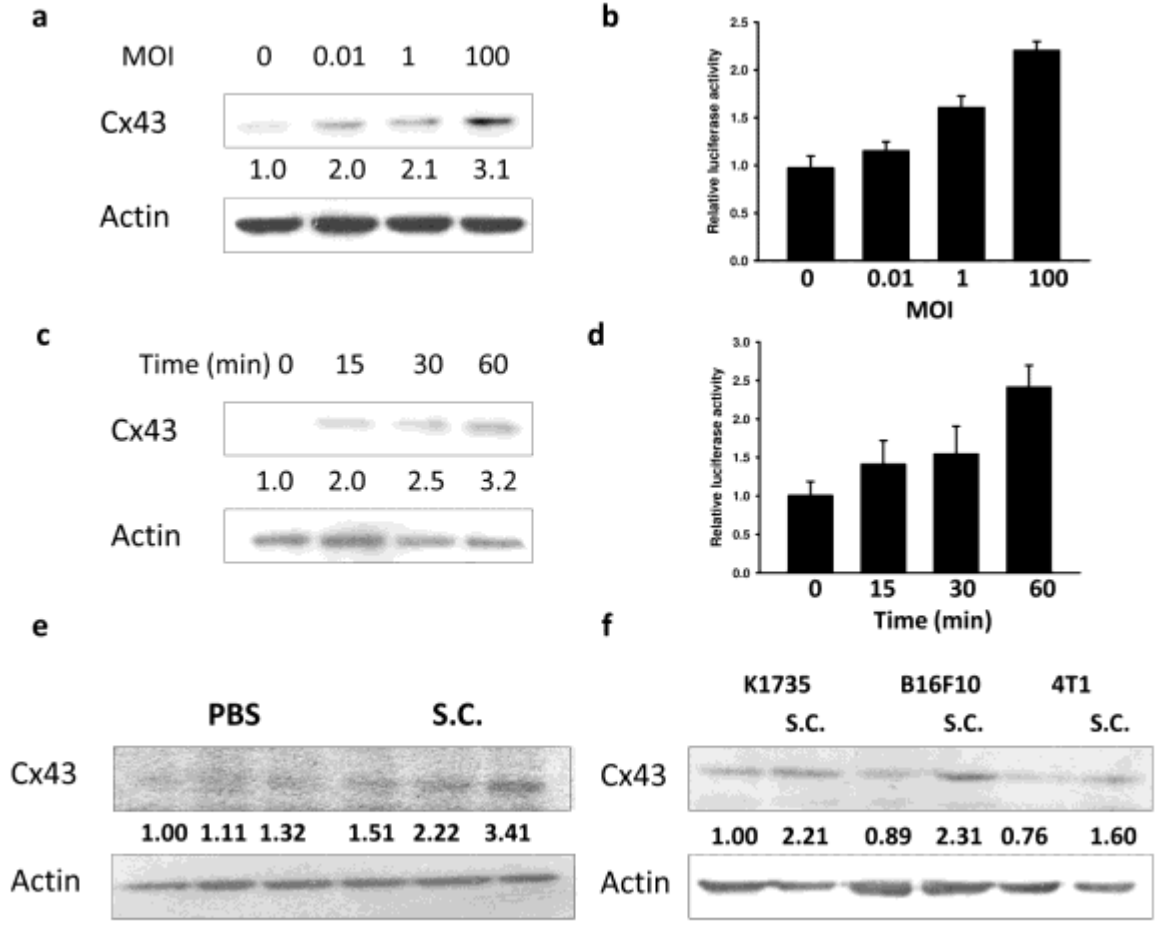
Increase in tumor cells undergoing apoptosis in LL2 tumor-bearing mice treated with *Salmonella* in combination with cisplatin



Mol. Ther. 11: 707, 2005.

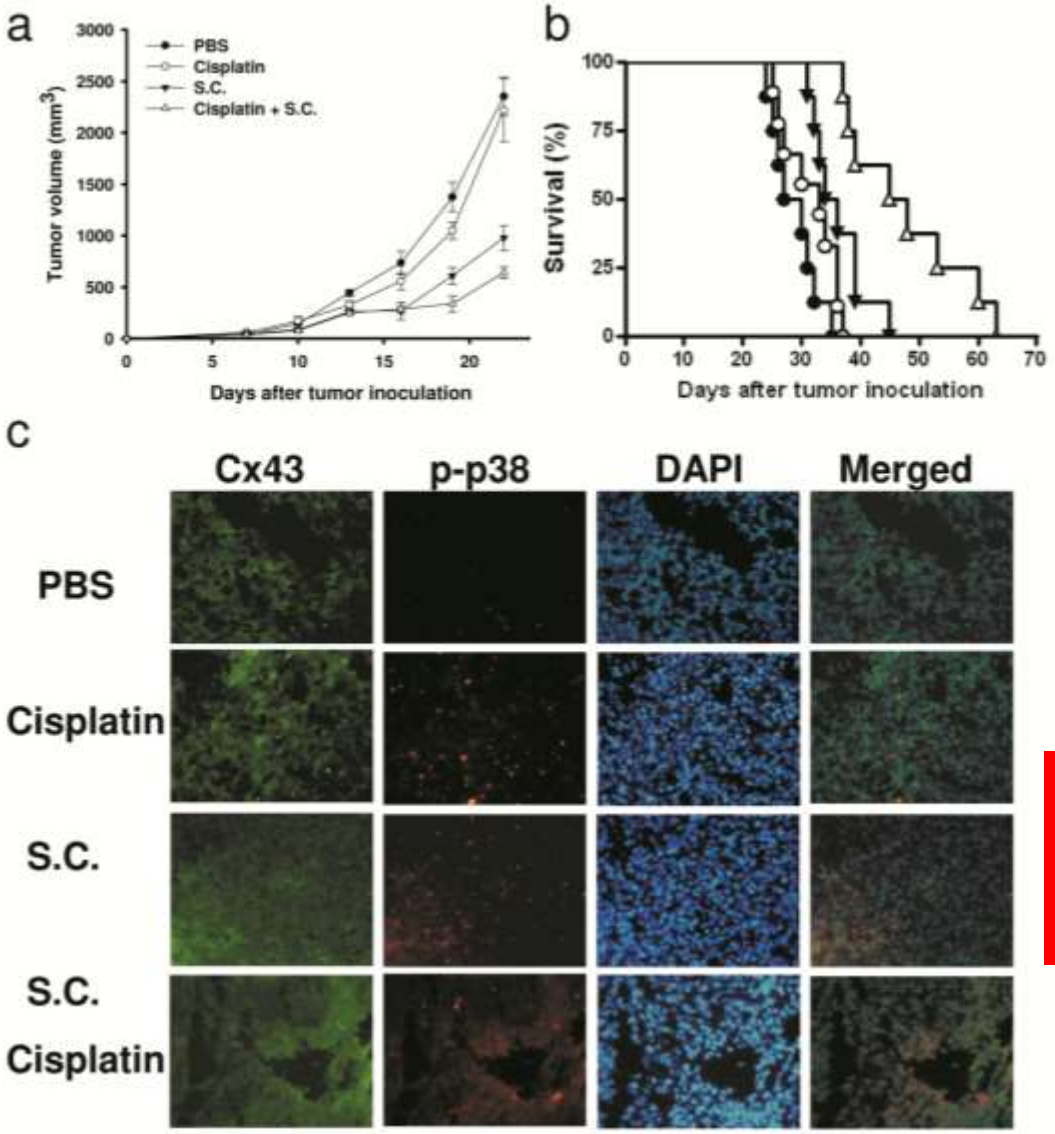
The combination therapy with *Salmonella* and low-dose cisplatin resulted in retarding tumor growth, increasing infiltrating neutrophils and $CD8^+$ T cells, as well as enhancing apoptosis in the tumors.

Salmonella induced Cx43 expression in tumors



Int. J. Cancer 133:1926, 2013.

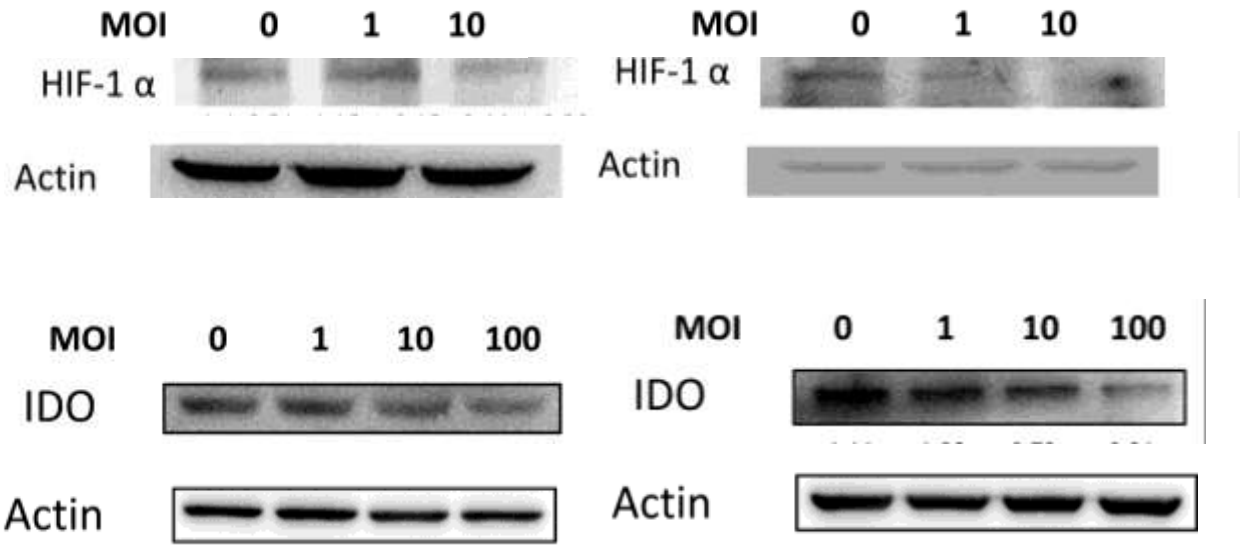
Additive antitumor effects of *Salmonella* in combination with cisplatin on subcutaneous K1735 tumors



Salmonella **enhance chemosentivity in tumor through Cx43 upregulation.**

Int. J. Cancer 133:1926, 2013.

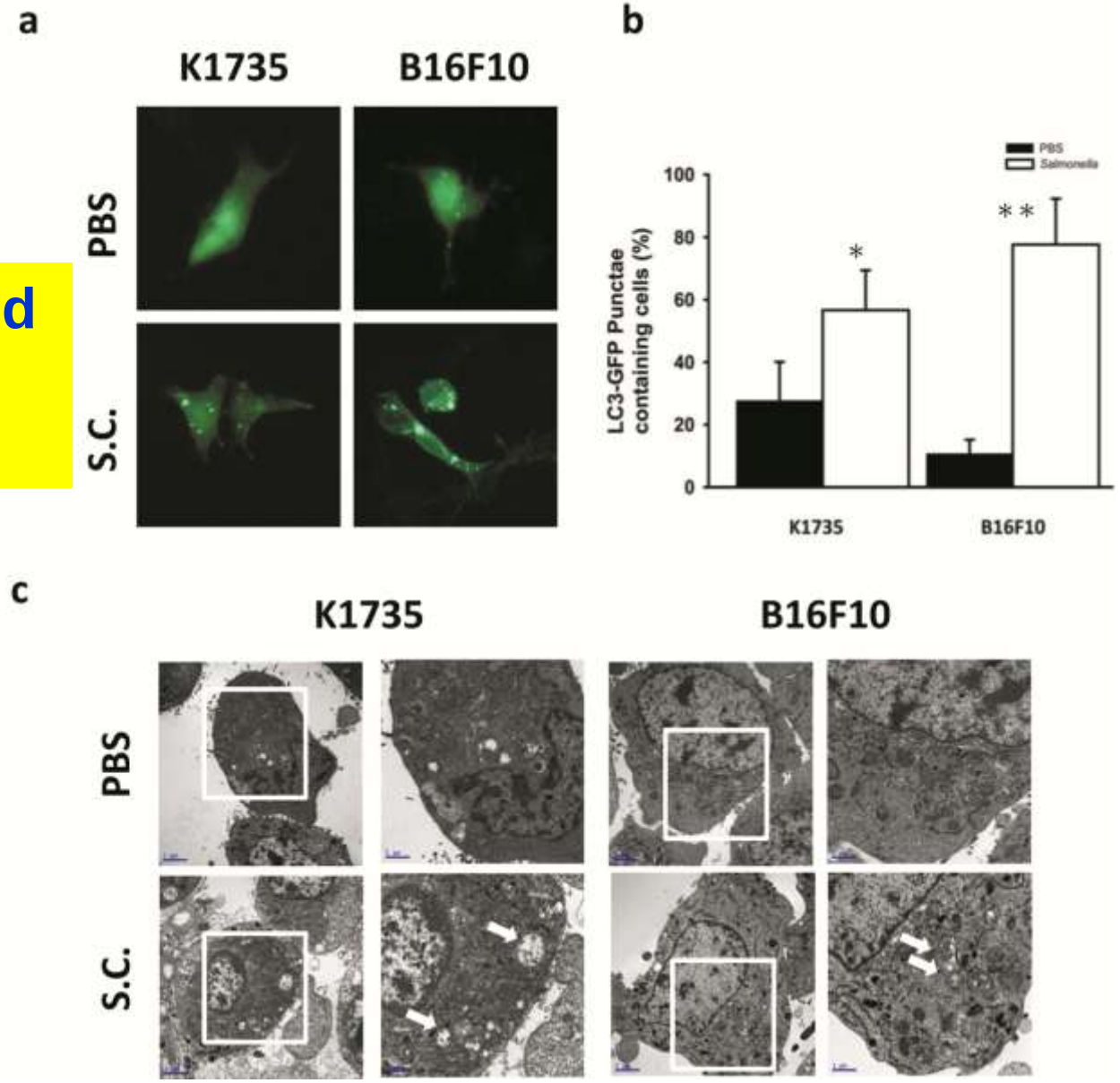
Salmonella reduced hypoxia-induced factor and indoleamine 2, 3-dioxygenase 1 expression in tumors



Oncotarget (in press)

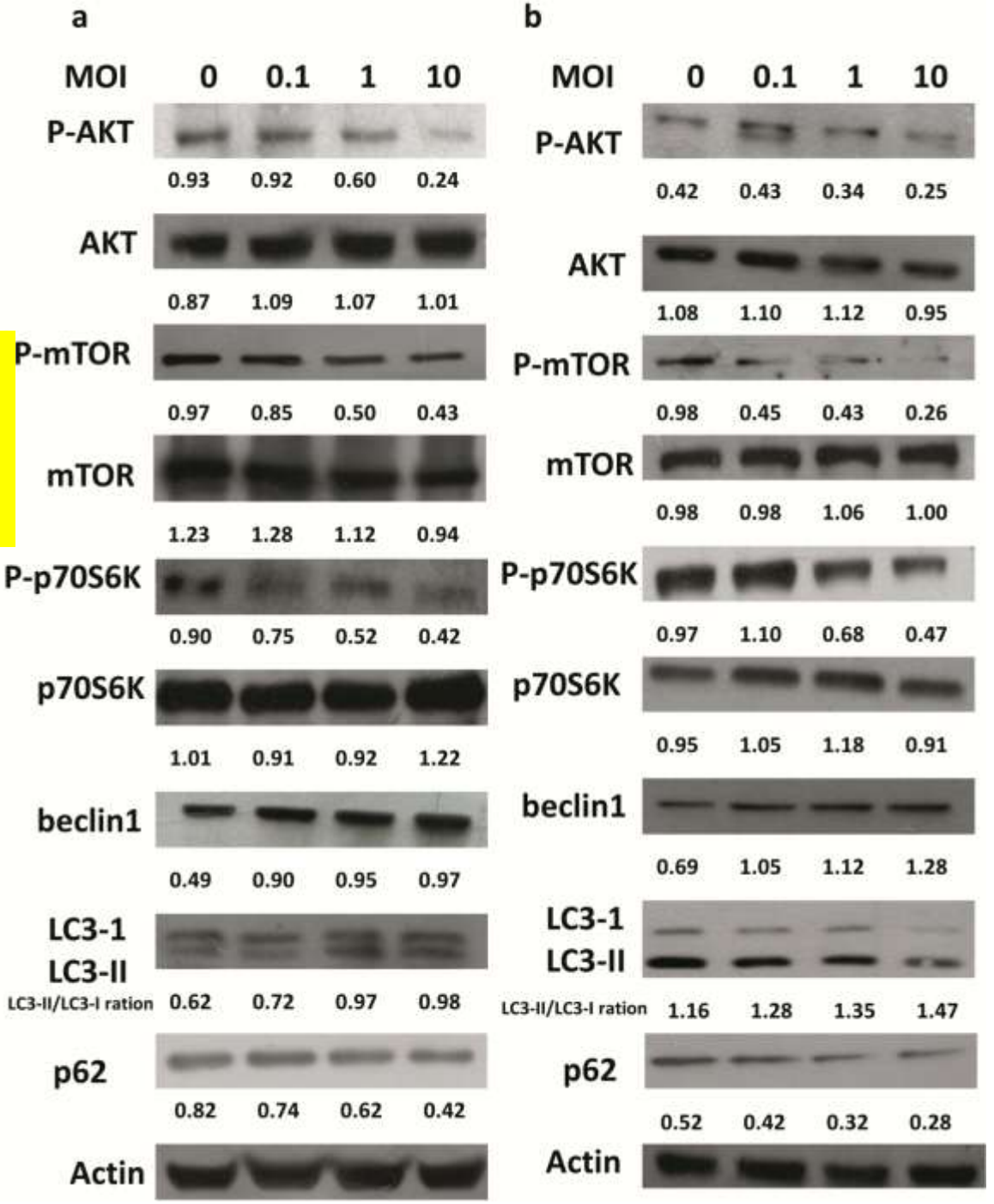
Oncotarget 7: 374, 2016.

***Salmonella* induced autophagy in melanoma cells.**



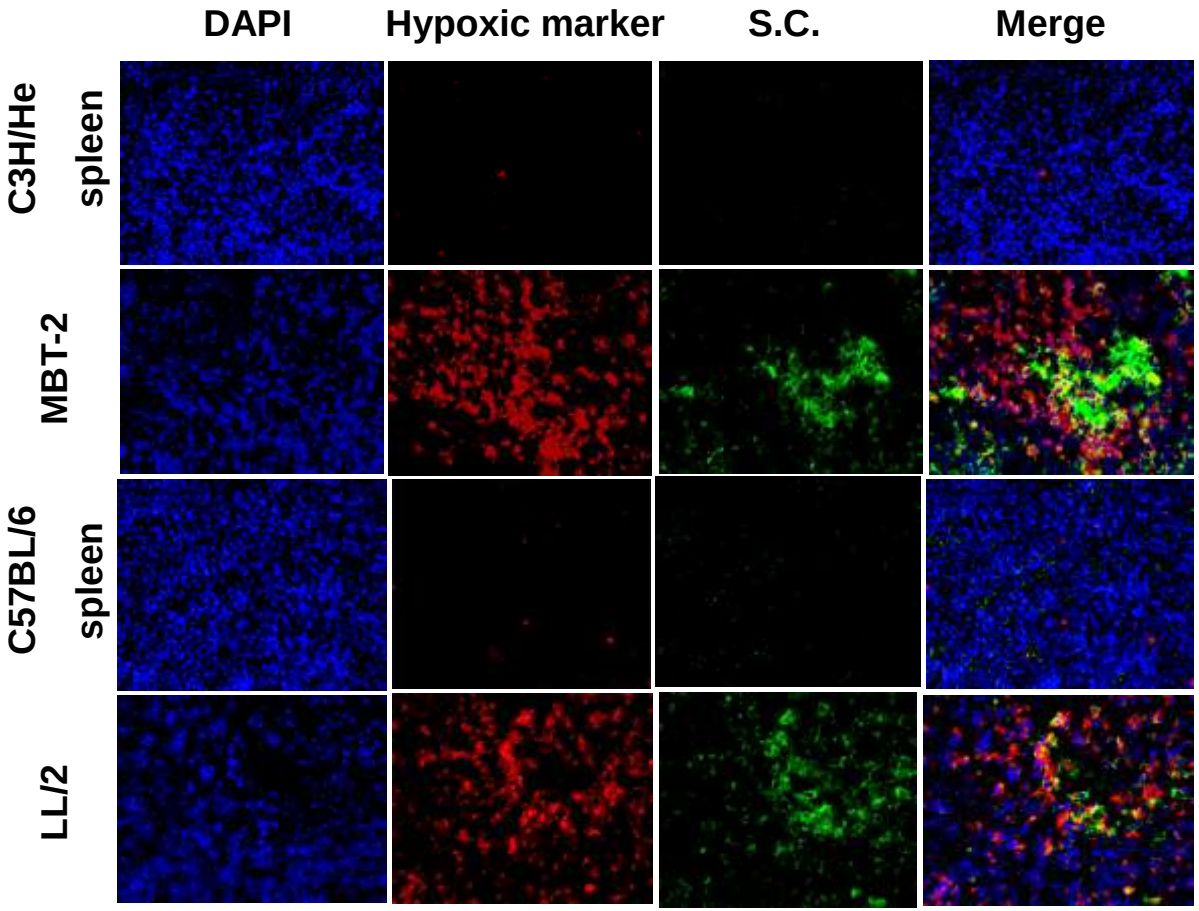
Gene Ther. 21: 309, 2014.

Salmonella induced autophagic signaling pathway



Gene Ther. 21: 309, 2014.

Salmonella colonization in the hypoxic regions of tumors



J. Gene. Med. 6: 1382, 2004.

Mol. Ther. 11: 707, 2005.

Tracking of mouse breast cancer stem-like cells with *Salmonella*

Isolation and characterization of Sca-1$^+$ 4T1 cell population

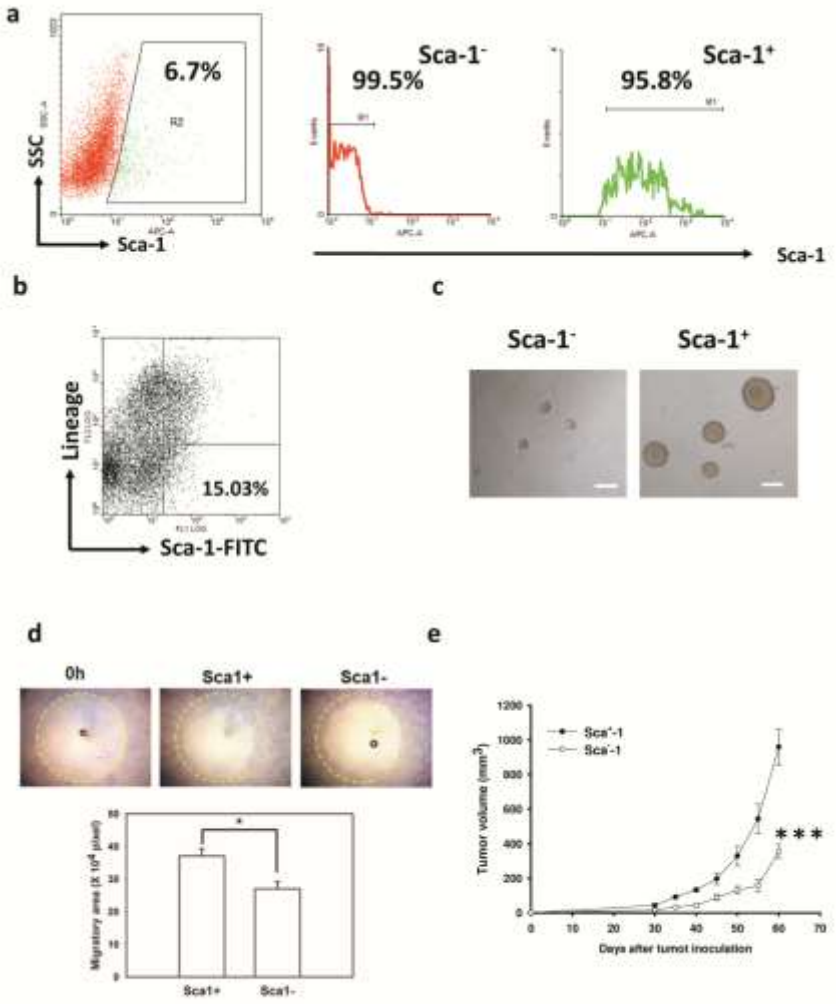
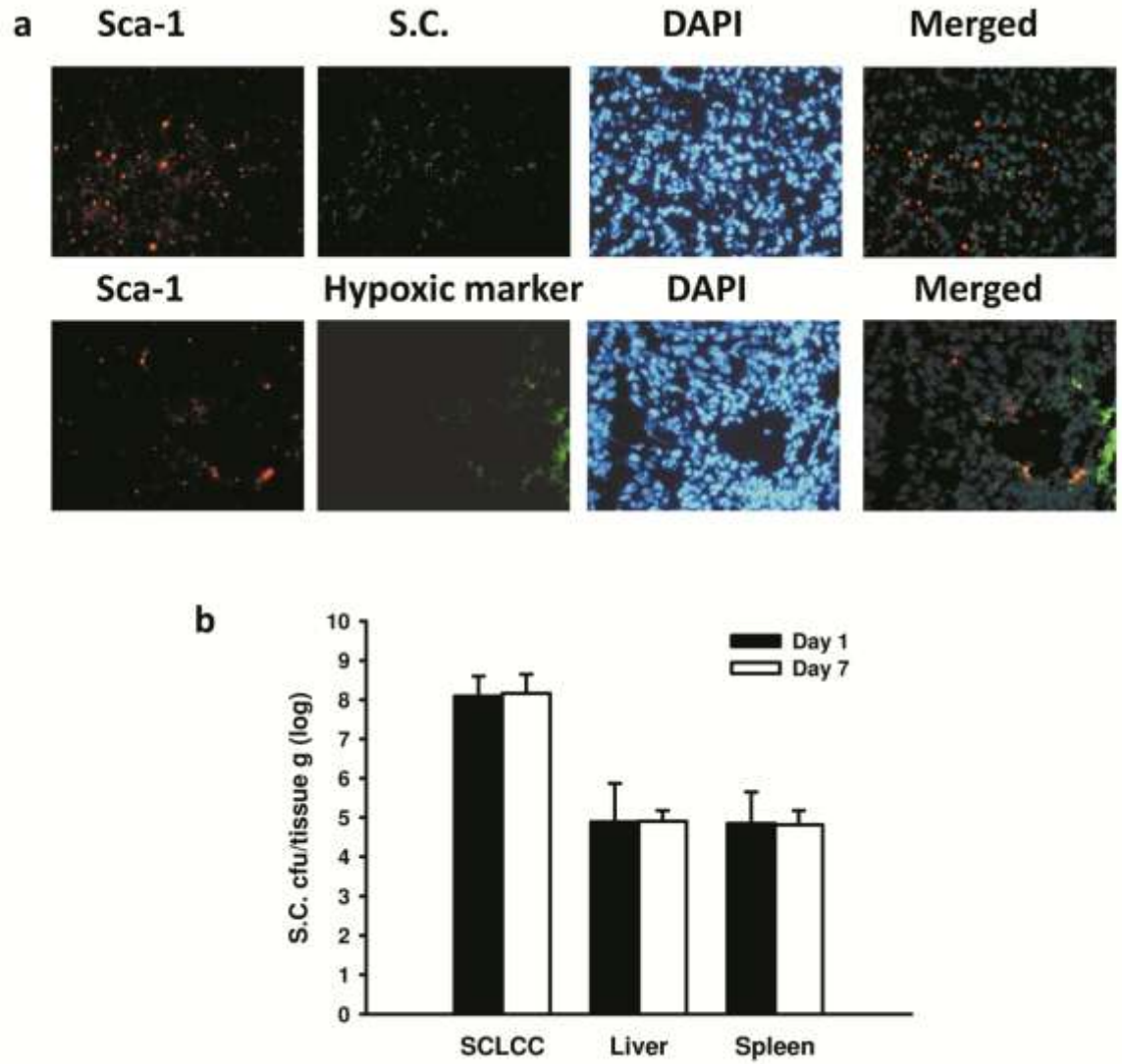


Table 1 Tumor-initiating ability of Sca-1$^+$ cells in mouse model

Cells	Number of injected cells		
	10^4	10^3	10^2
Sca-1$^+$	5/5	5/5	2/5
Sca-1$^-$	5/5	2/5	0/5

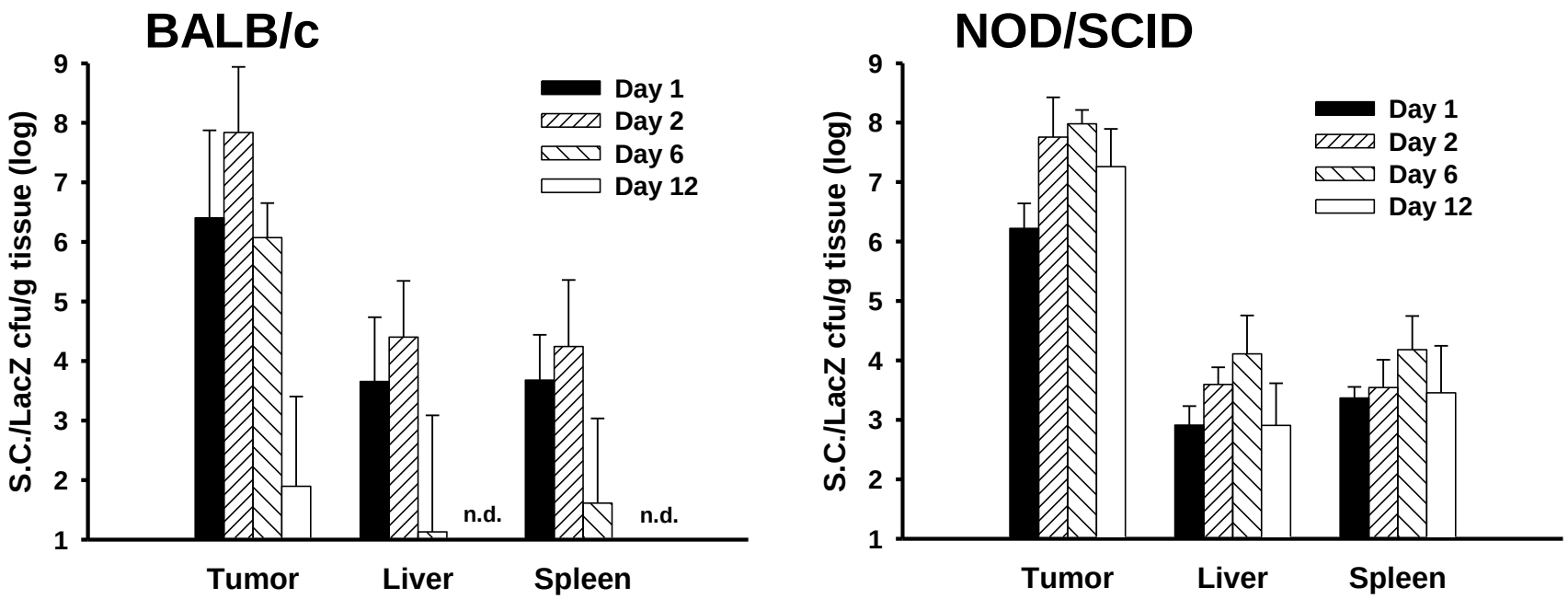
Exp. Biol. Med. 237:1189, 2012.

Bacterial colonization in the CSC niche



Exp. Biol. Med. 237:1189, 2012.

The distribution of *Salmonella* in immunocompetent and immunodeficient mice

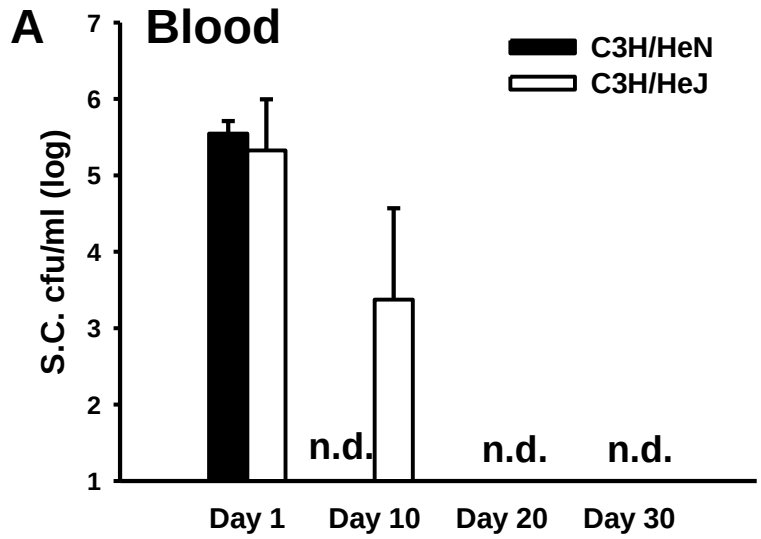


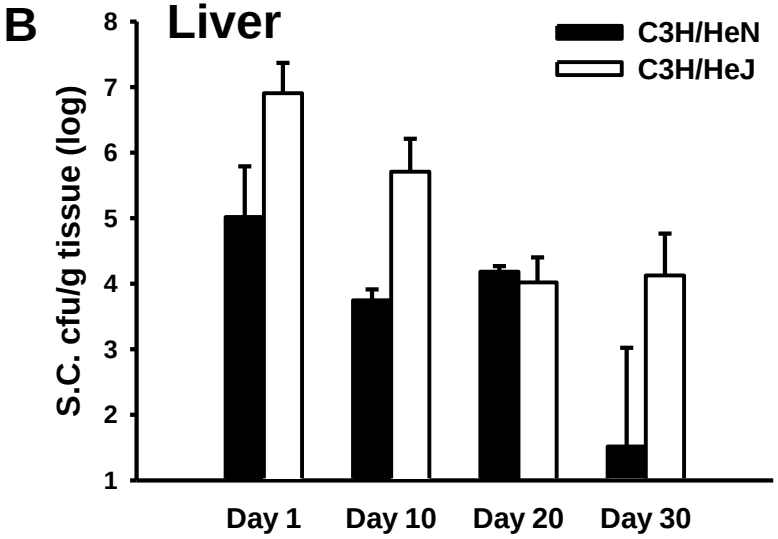
J. Gene. Med. 6: 1382, 2004.

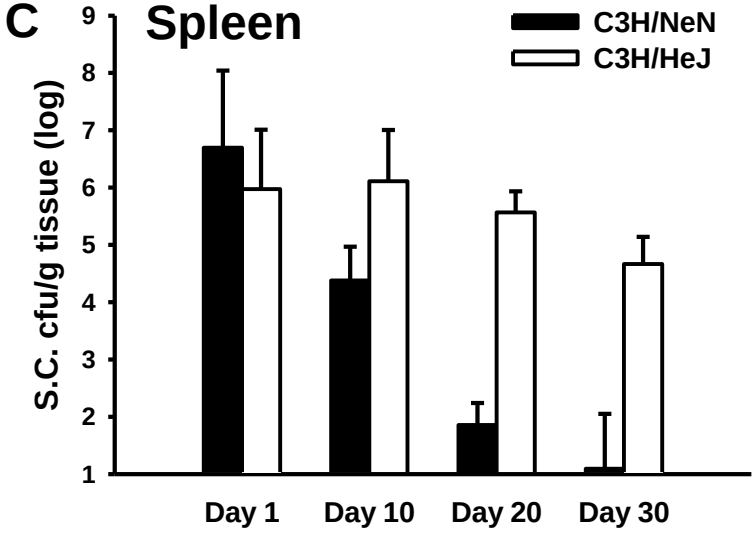
The tumor microenvironment may contribute to the preferential accumulation of *Salmonella* in tumors.

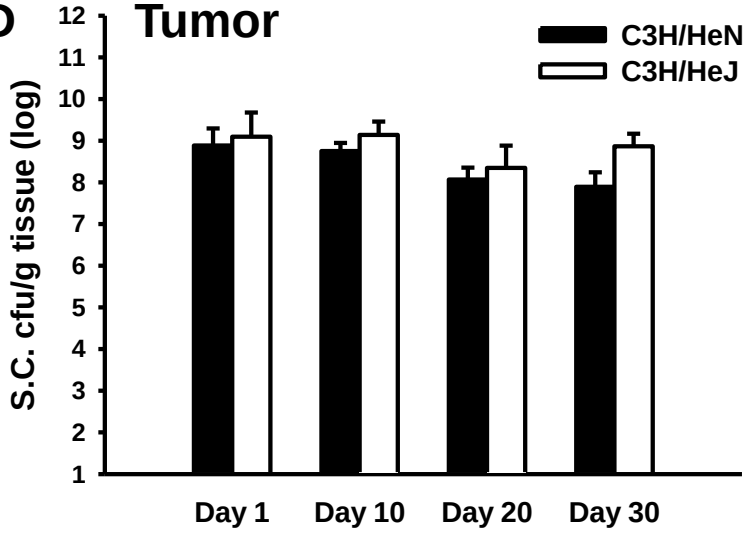
Toll-like Receptor 4 Mediates an Antitumor Host Response Induced by *Salmonella choleraesuis*

Temporal distribution of *Salmonella* in wild-type and Toll like receptor 4 (TLR4) defective mice



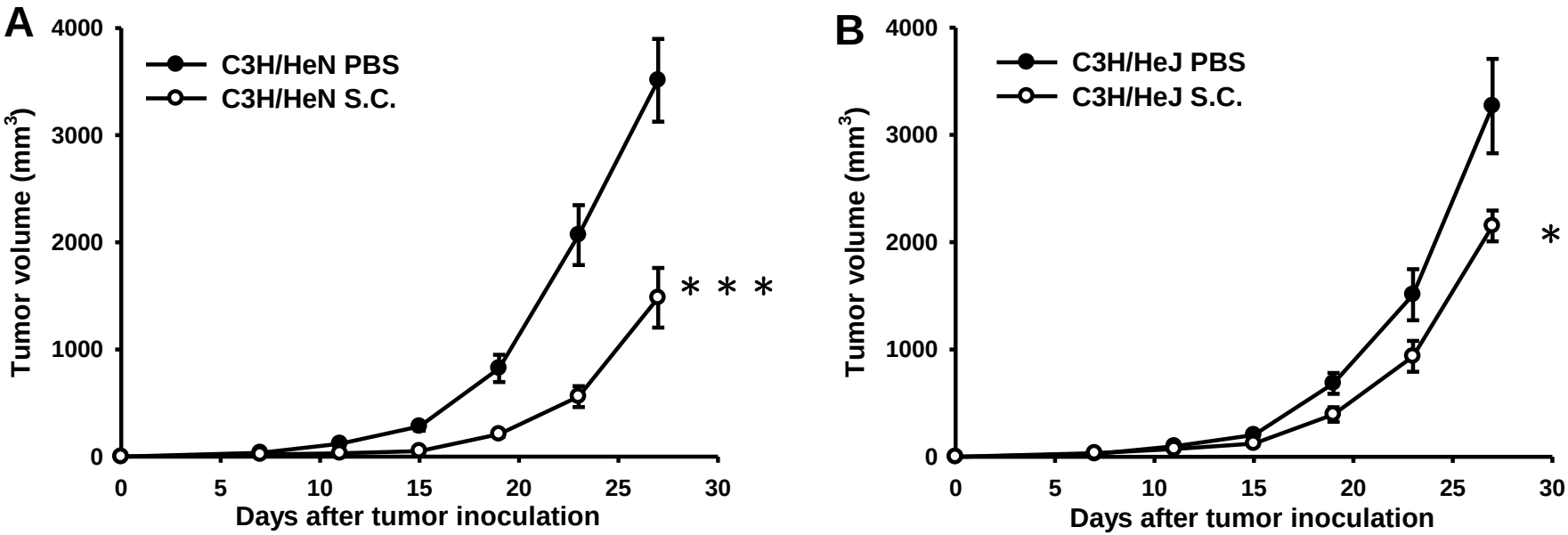






Clin. Cancer Res. 14:1905, 2008.

Antitumor effects of *Salmonella* on wild-type and TLR4 defective mice

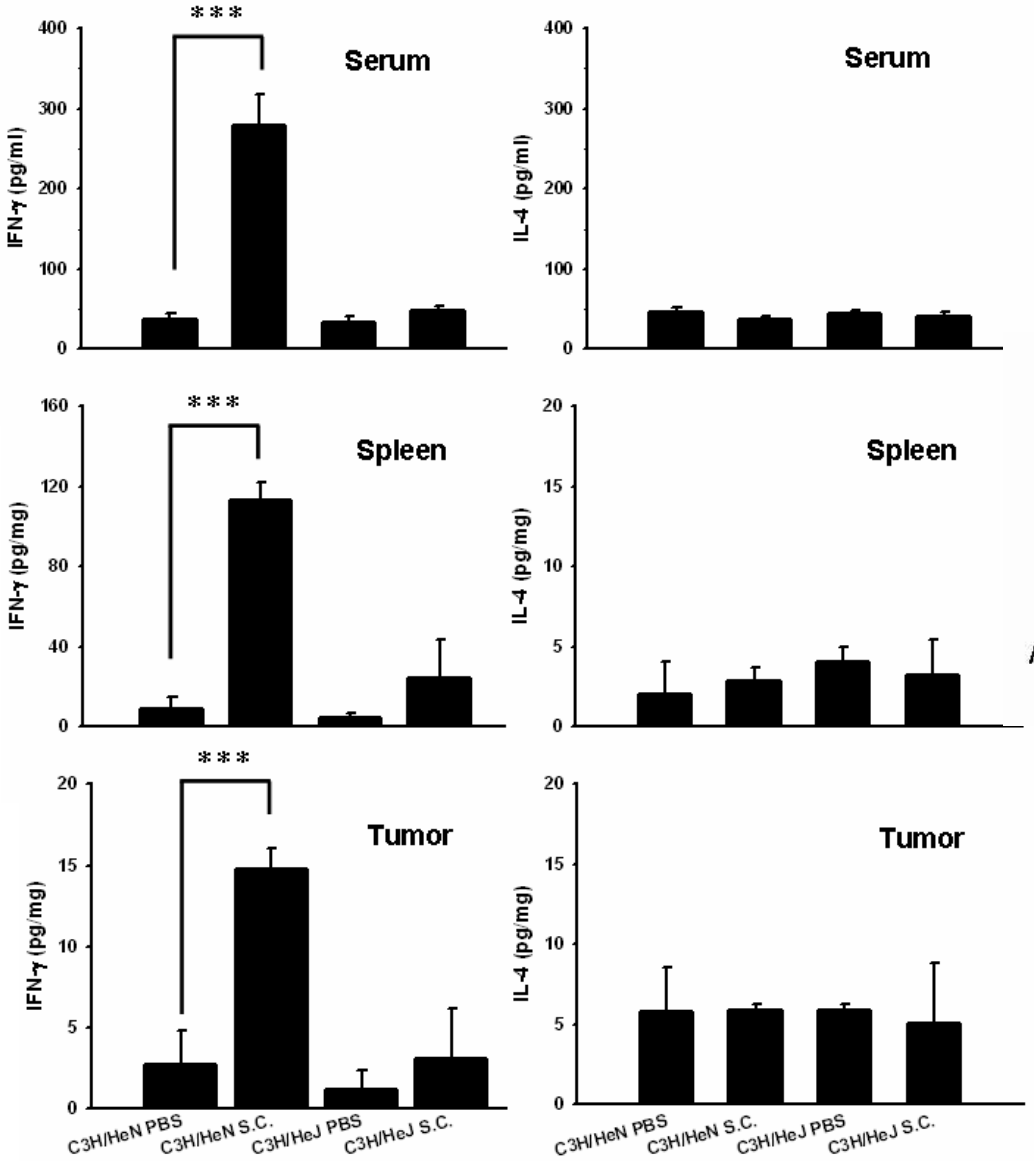


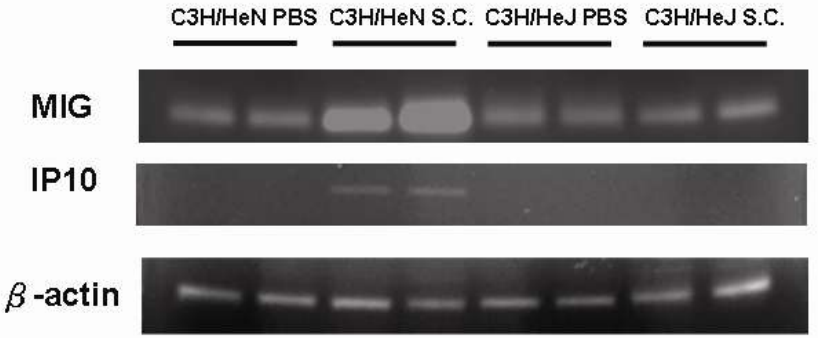
The mean tumor volumes in C3H/HeN mice treated with *S. choleraesuis* was lowered by 57.79% compared with those treated with PBS, but that was lowered by 34.19 % in C3H/HeJ mice.

Clin. Cancer Res. 14:1905, 2008.

TLR 4 signaling influenced the antitumor effects of *Salmonella*.

Effects of *Salmonella* on cytokines and chemokines induction in vivo

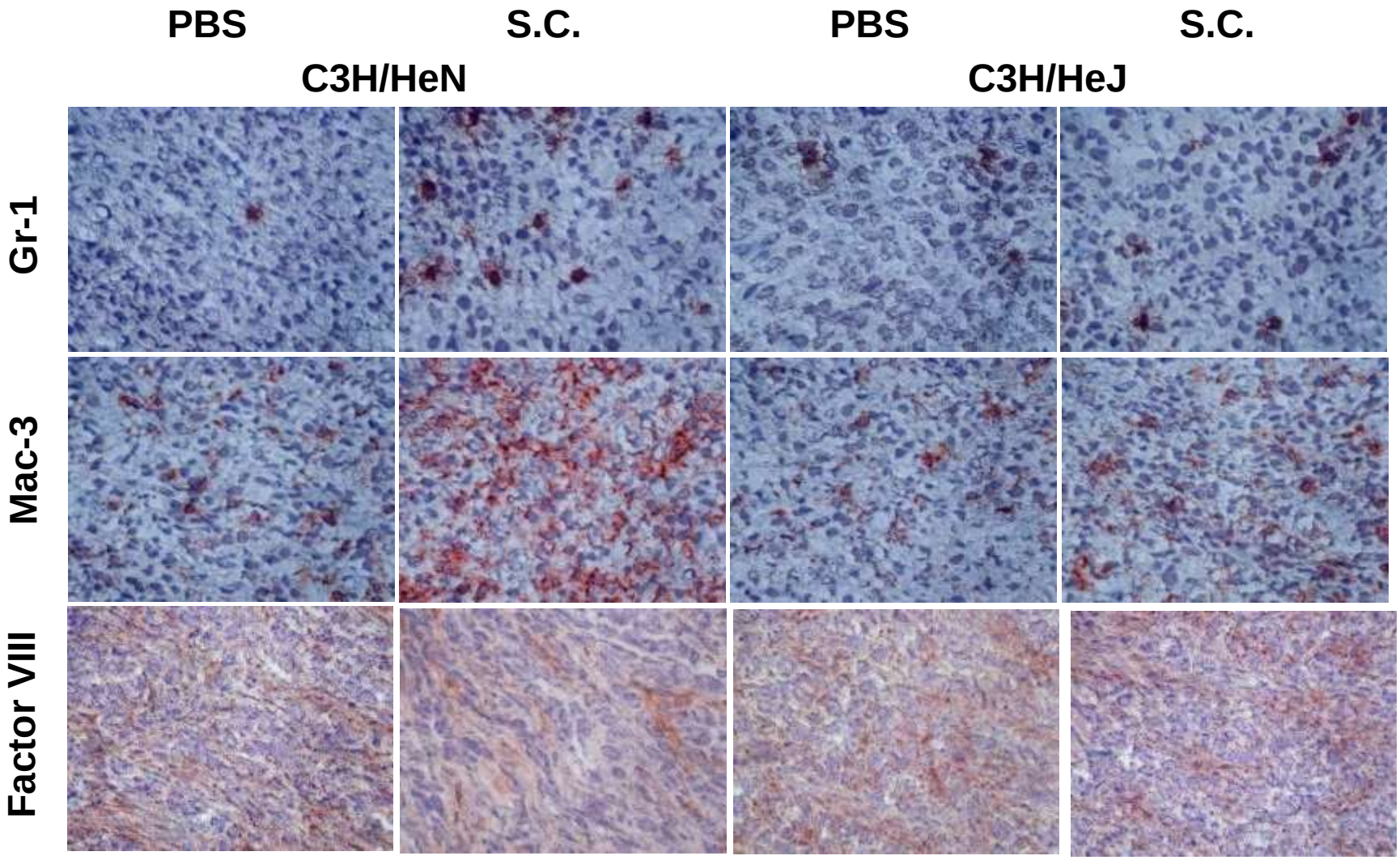




Salmonella **elicited IFN-γ and IFN-γ-inducing responses via TLR 4 signaling.**

Clin. Cancer Res. 14:1905, 2008.

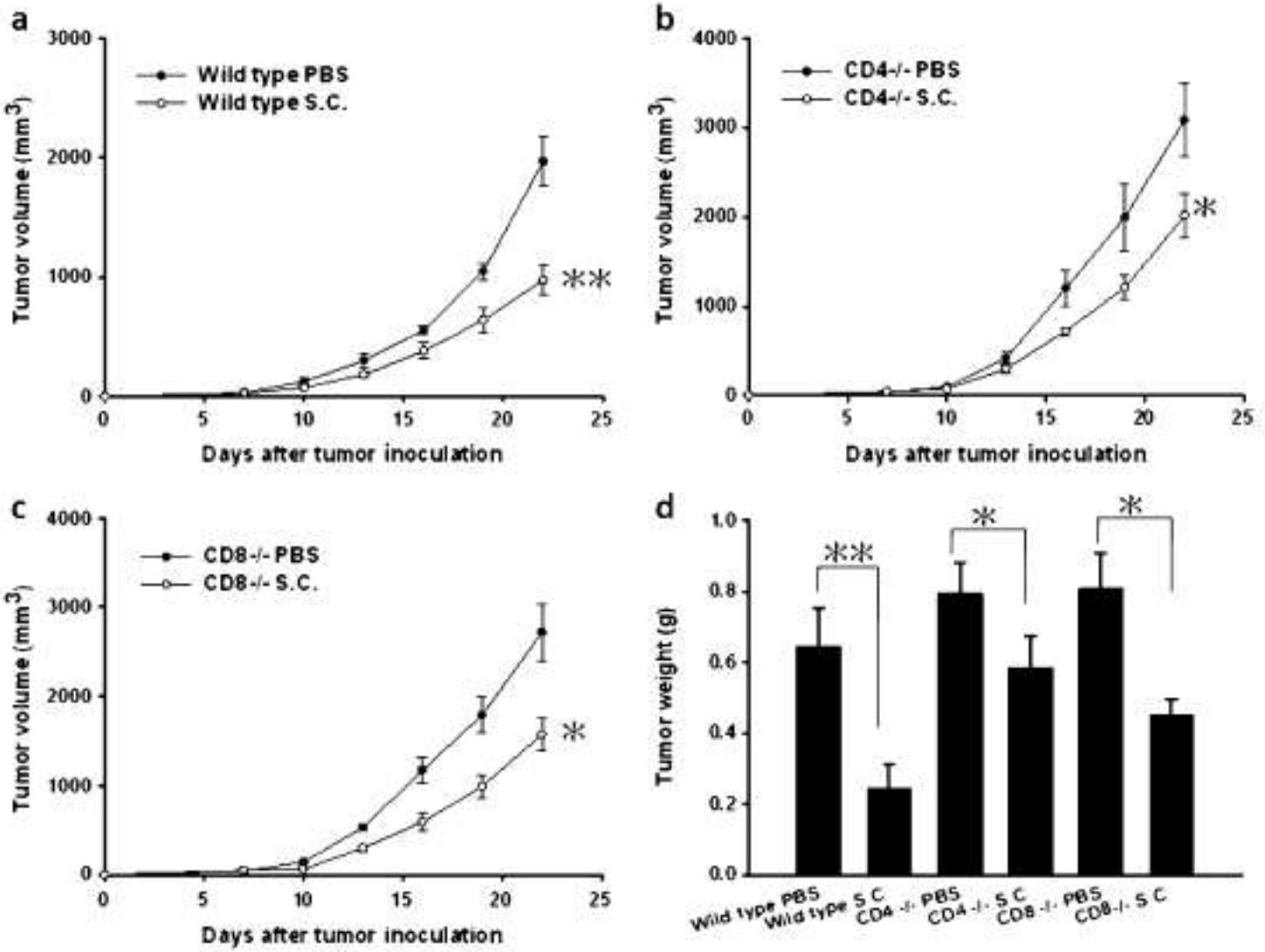
Effects of *Salmonella* on chemokine induction in wild-type and TLR4 defective mice



Clin. Cancer Res. 14:1905, 2008.

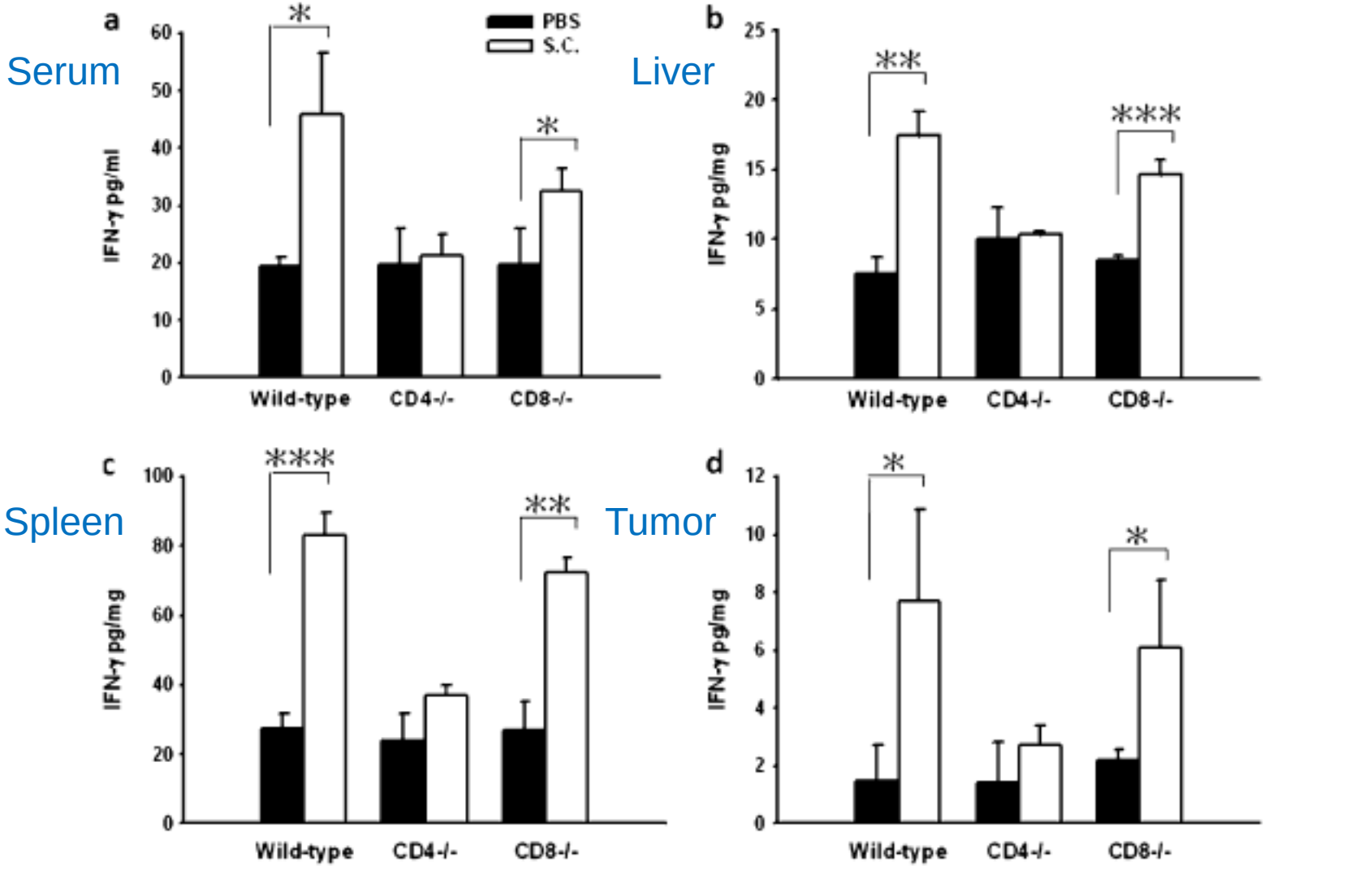
T cell augments the antitumor activity of tumor-targeting *Salmonella*

Antitumor effects of *Salmonella* on tumor growth in T-cell-deficient and wild-type mice bearing tumors



Appl. Microbiol. Biotechnol. 90: 1381, 2011.

Effects of *Salmonella* on cytokine induction in T-cell-deficient and wild-type mice bearing tumors

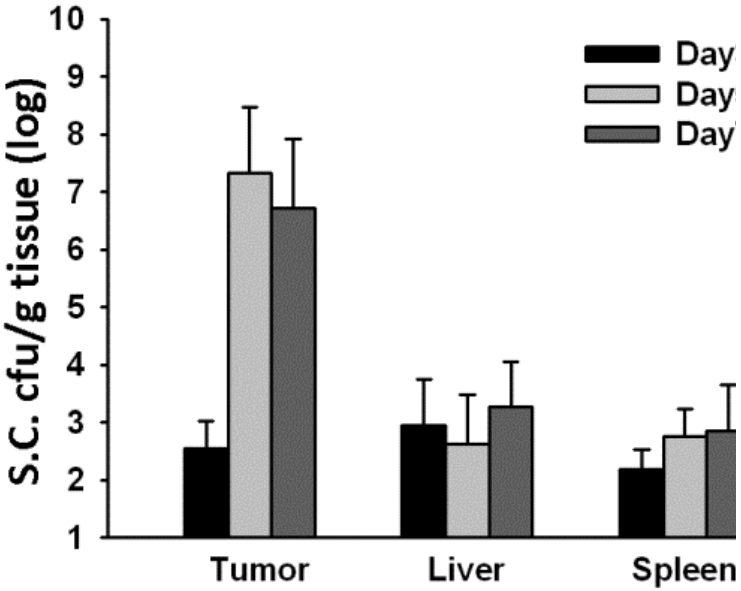


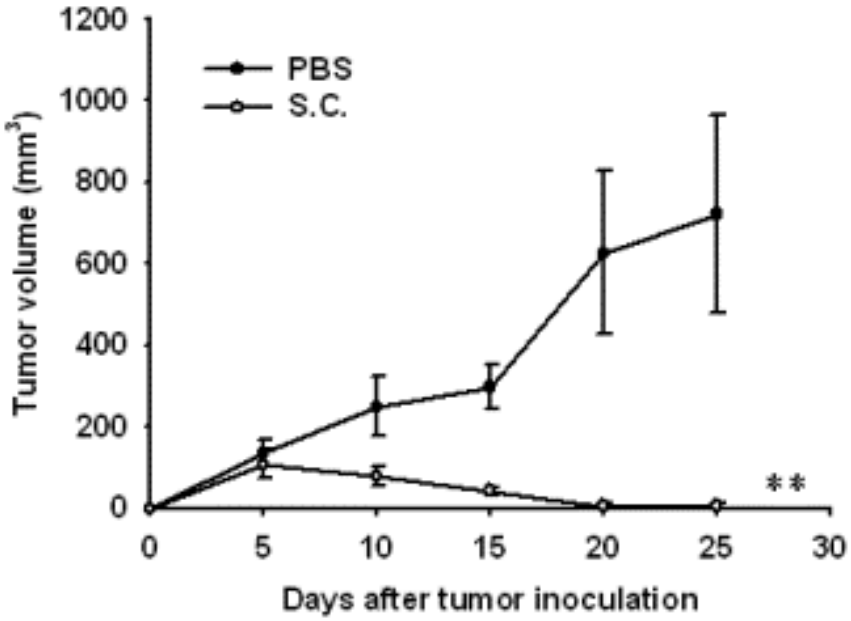
Appl. Microbiol. Biotechnol. 90: 1381, 2011.

Biodistribution of *Salmonella*

Tumor cells	Liver / Tumor ratio	animal model
MBT-2	1:1000~1:10000	C3H/HeN
K1735	1:1000~1:1000000	C3H/HeN
B16F10	1:1000~1:10000	C57BL/6
LL2	1:1000~1:1000000	C57BL/6
4T1	1:1000~1~100000	BALB/c
ML-1	1:10000~1:100000	BALB/c
A549	1:1000~1:10000	NOD/SCID
PC14PE6	1:1000~1:10000	NOD/SCID

Oral administration of *Salmonella*





Am. J. Can. Res. 5: 2222, 2015.

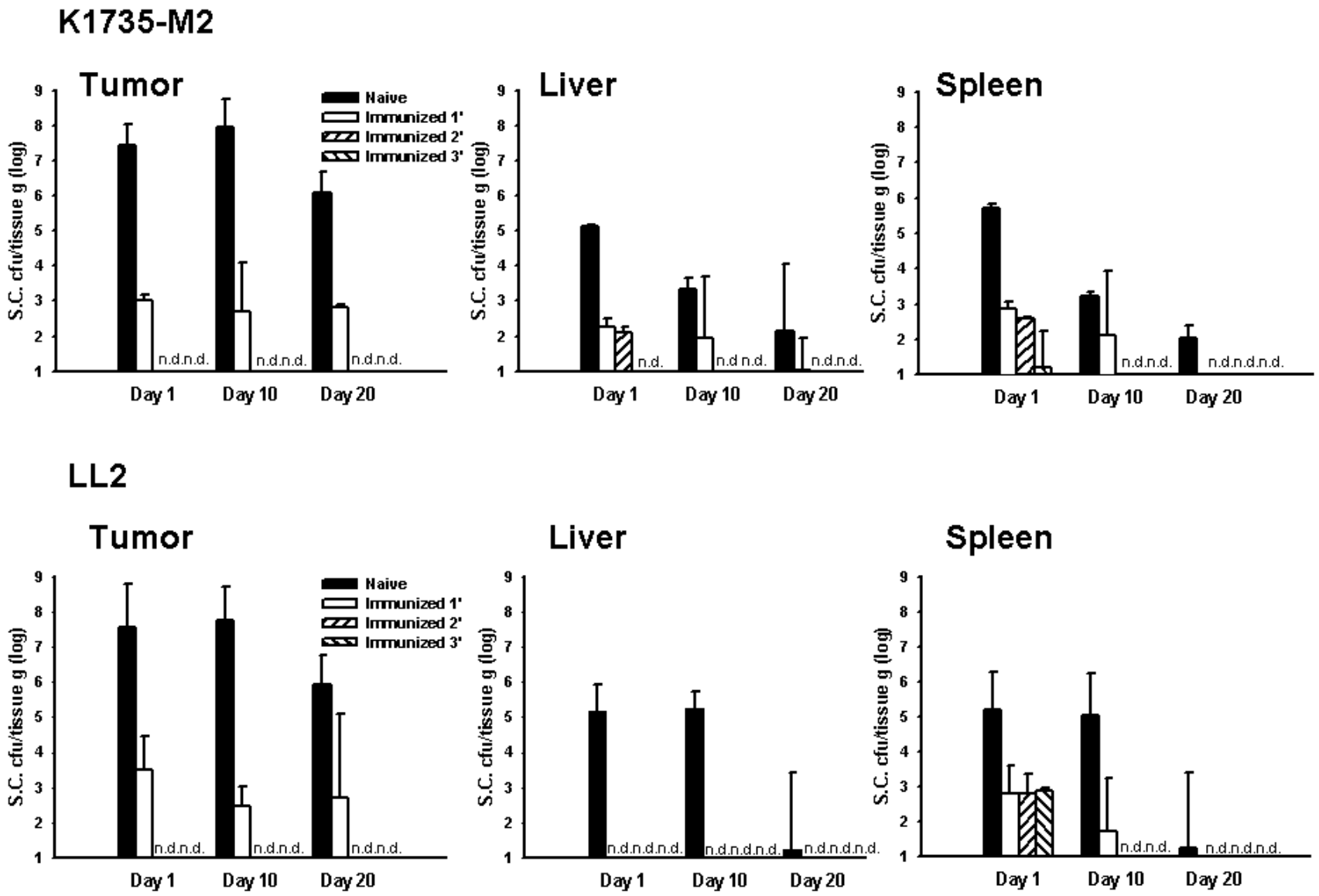
Clinical trial

Toso JF, Gill VJ, Hwu P, et al. Phase I study of the intravenous administration of attenuated *Salmonella typhimurium* to patients with metastatic melanoma. J Clin Onco. 2002;20:142-52.

Heimann DM, Rosenberg SA. Continuous intravenous administration of live genetically modified *Salmonella typhimurium* in patients with metastatic melanoma. J Immunother. 2003;26:179-80.

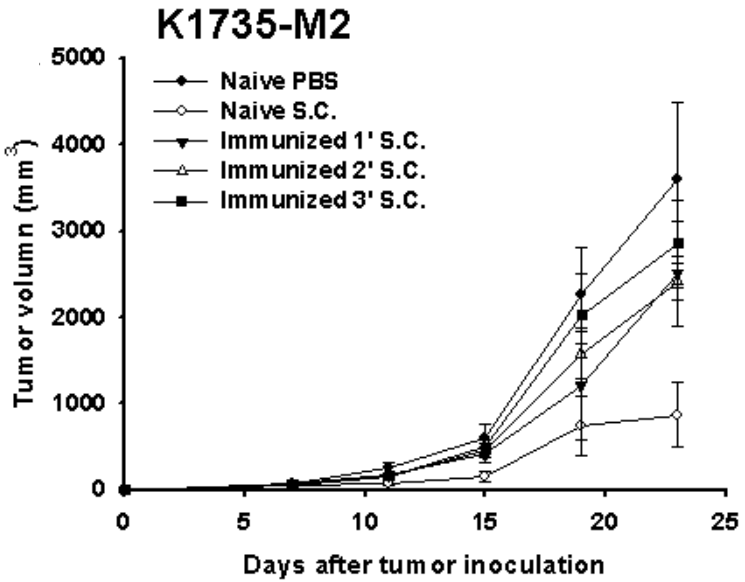
Humoral Immune Responses Inhibit the Antitumor Activities Mediated by *Salmonella enterica* serovar Choleraesuis

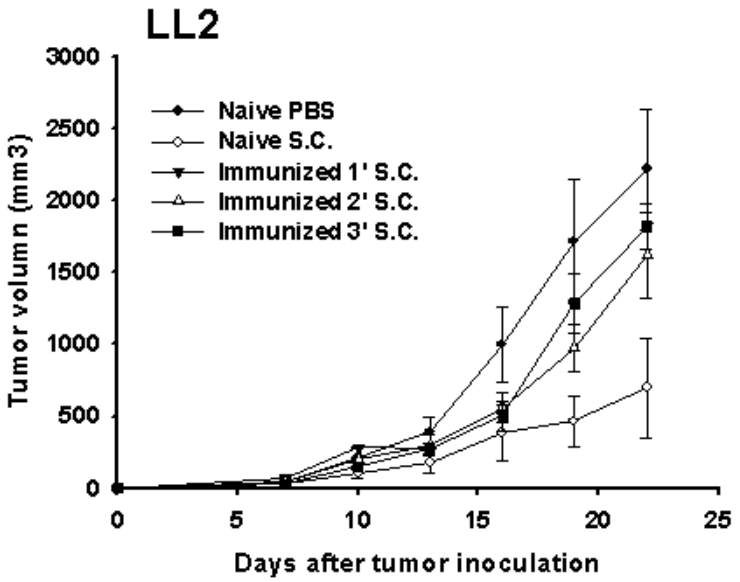
Tissue distributions of *Salmonella* in naive and immunized mice

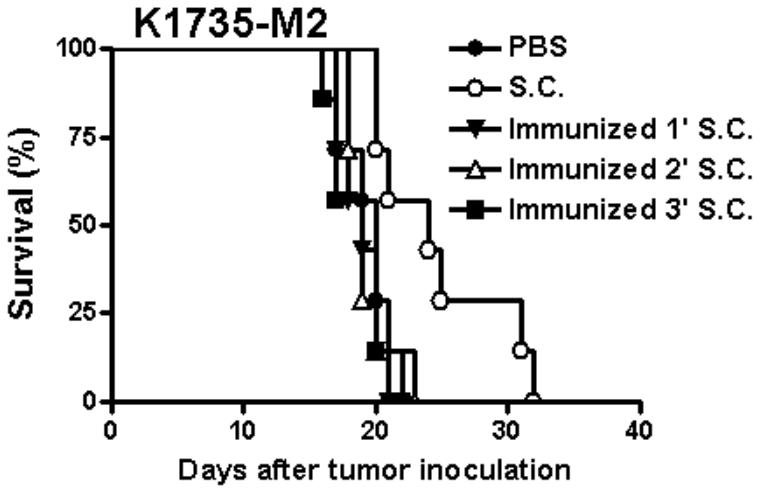


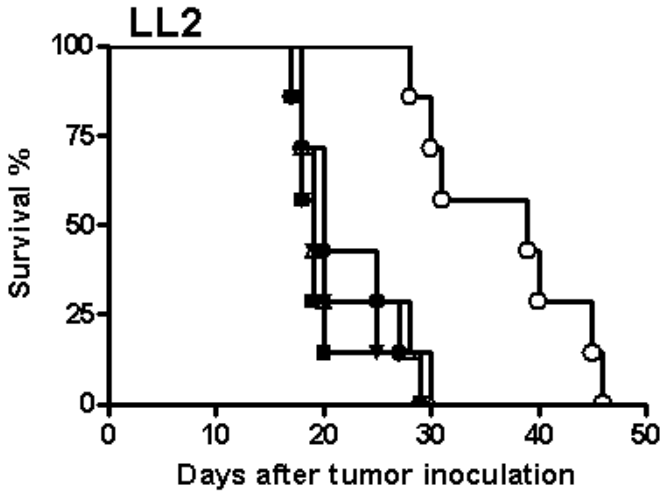
J. Immunother. 32: 376, 2009.

Antitumor effects of *Salmonella* on the naive and immunized mice









J. Immunother. 32: 376, 2009.

A polymer coating applied to *Salmonella* prevents the binding of *Salmonella*-specific antibodies

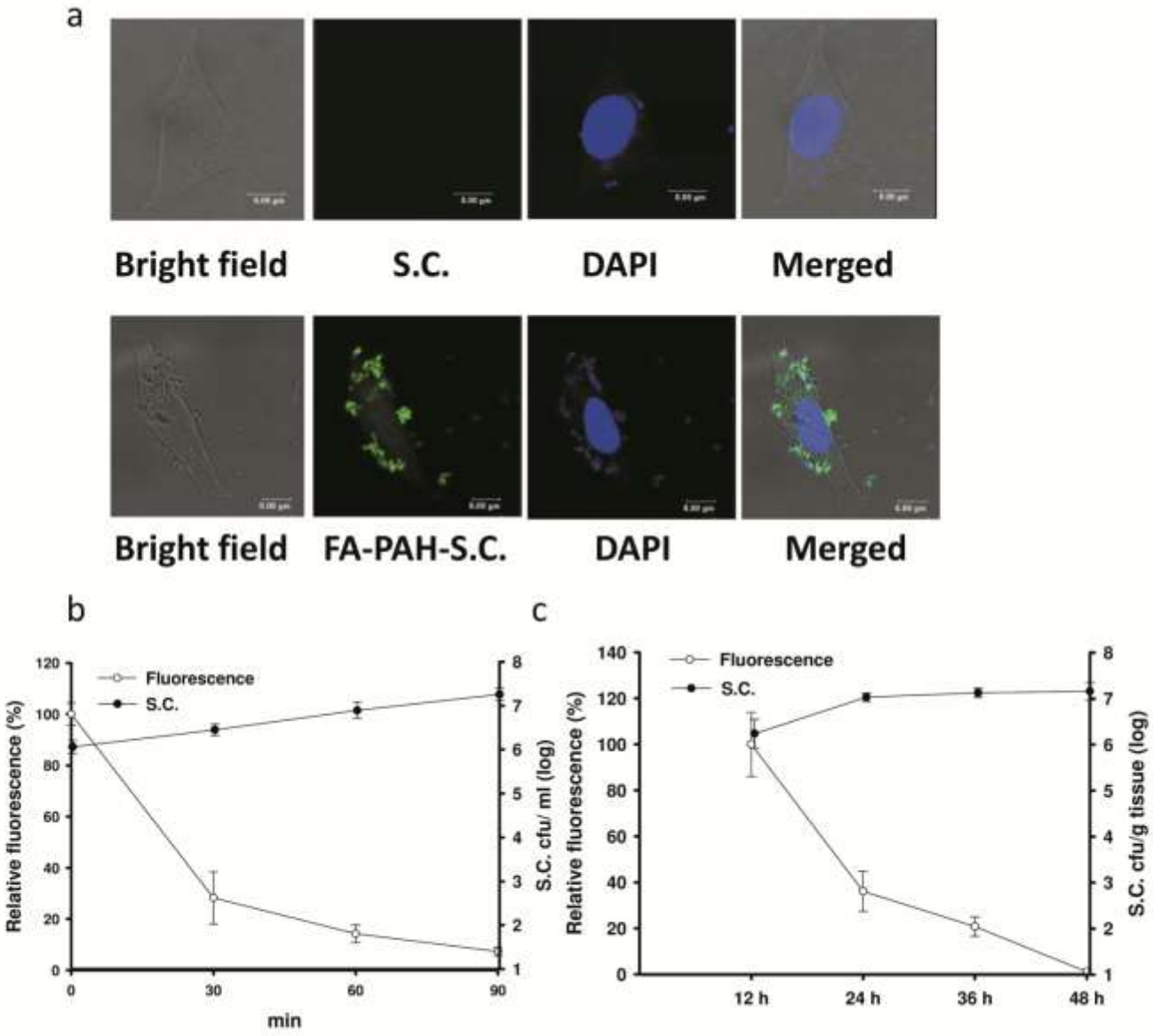
Characterization of poly(allylamine hydrochloride) (PAH)-modified *Salmonella*

Table 1. Particle sizes and zeta potential values of PAH-S.C. particles prepared with different PAH concentrations in deionized water ($n = 5$)

PAH concentration (mg/ml)	Particle size (nm)	Zeta potential (mV)
0	938.13 ± 84.69	−4.70 ± 2.45
1.25	1281.14 ± 71.61	−0.7469 ± 2.04
5	1180.57 ± 63.76	4.22 ± 1.18
20	1260.55 ± 180.33	11.75 ± 0.31

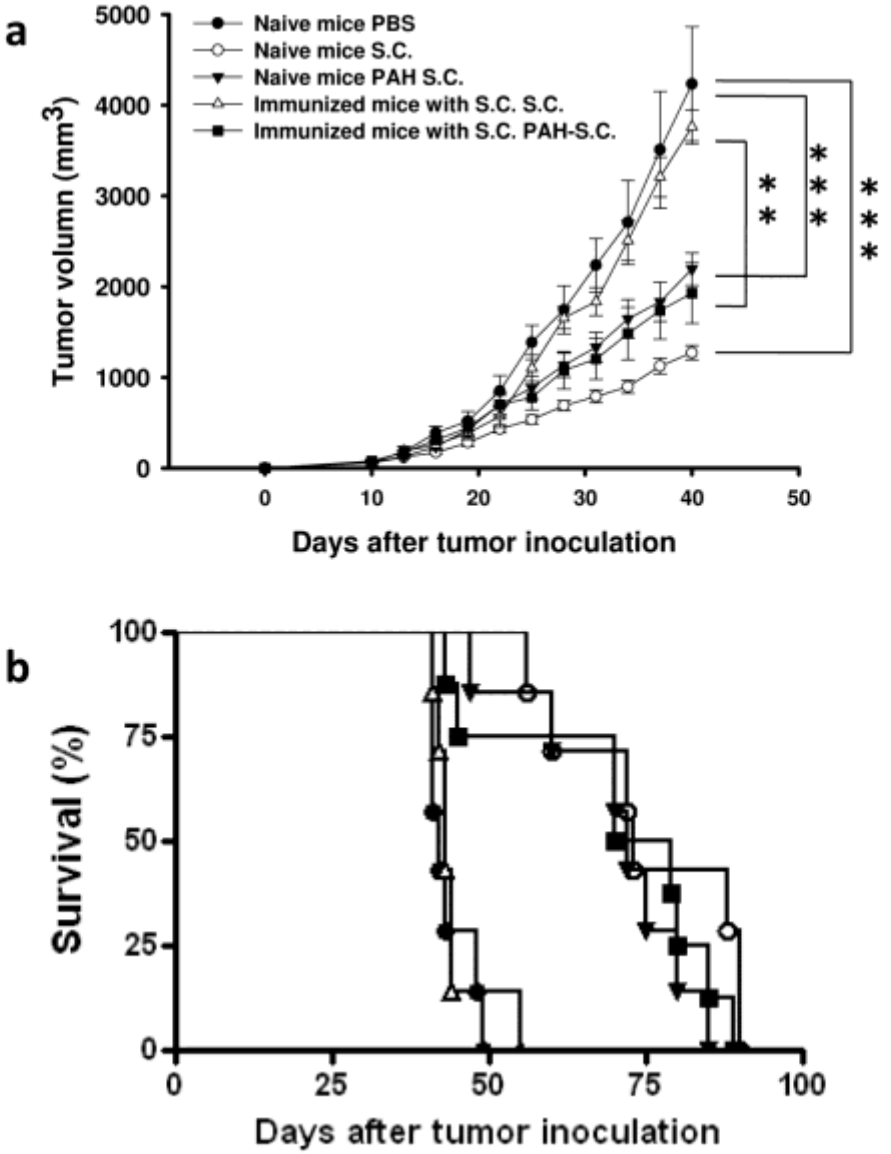
Int. J. Cancer 133: 1926, 2013.

Inhibition of tumor growth by PAH-modified *Salmonella*



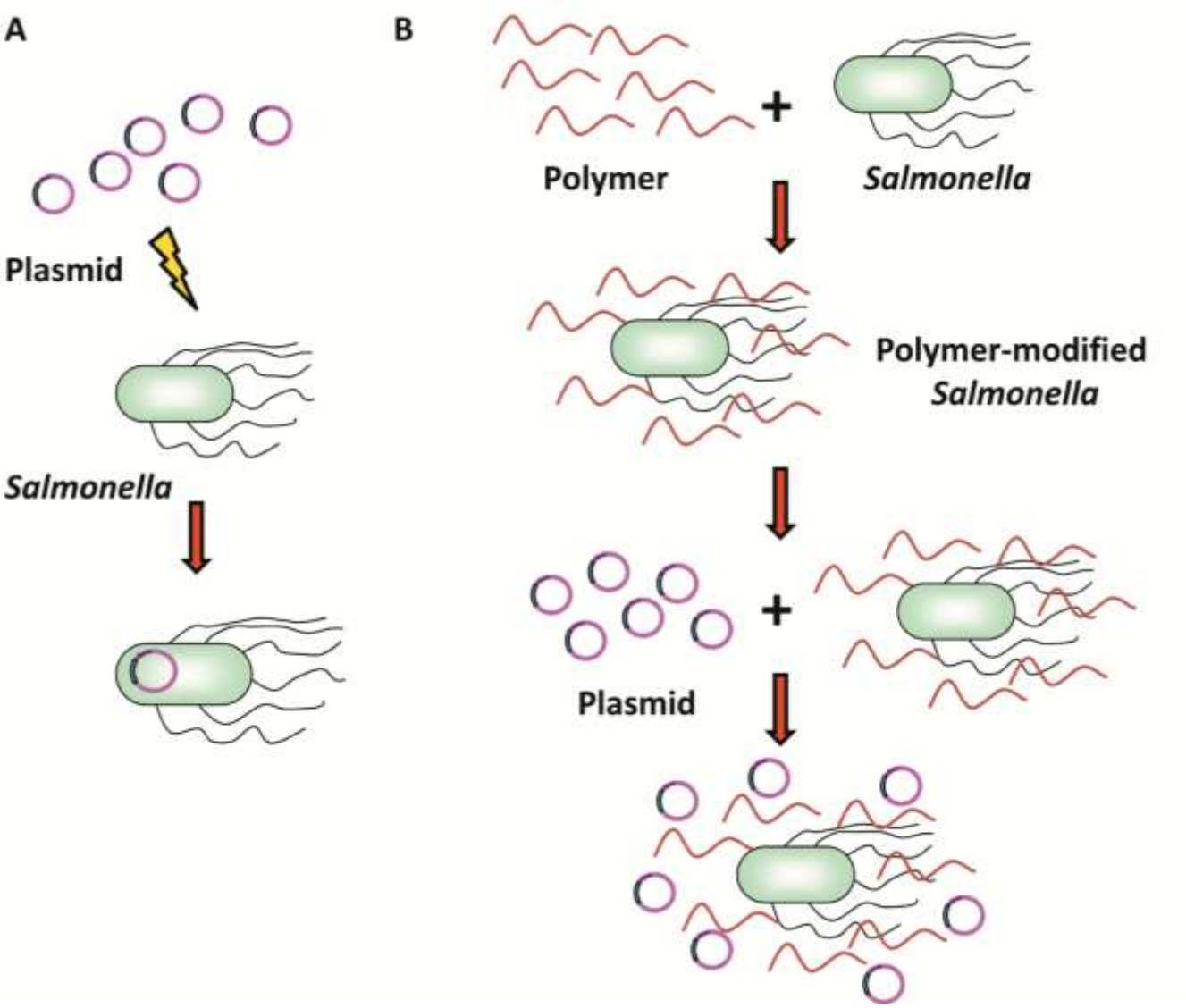
Int. J. Cancer 133: 1926, 2013.

Inhibition of tumor growth by PAH-modified *Salmonella*



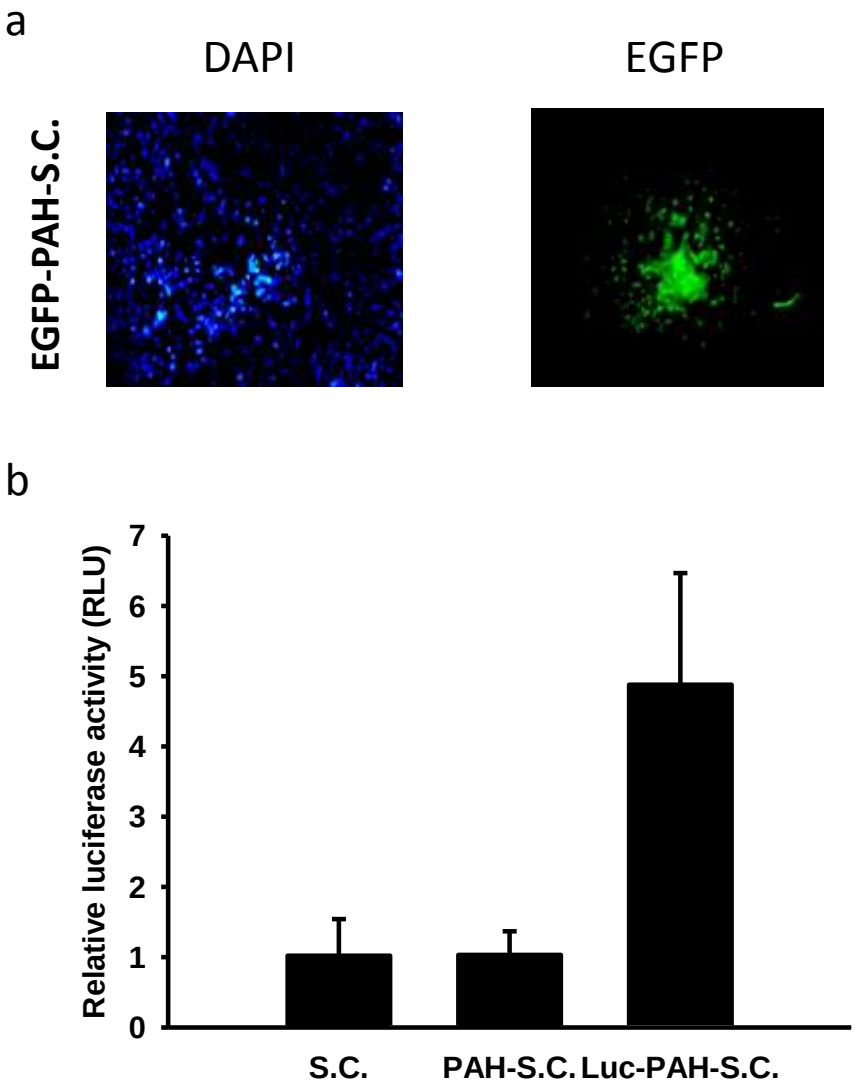
Int. J. Cancer 133: 1926, 2013.

The strategy of preparation of *Salmonella* carrying *DNA*



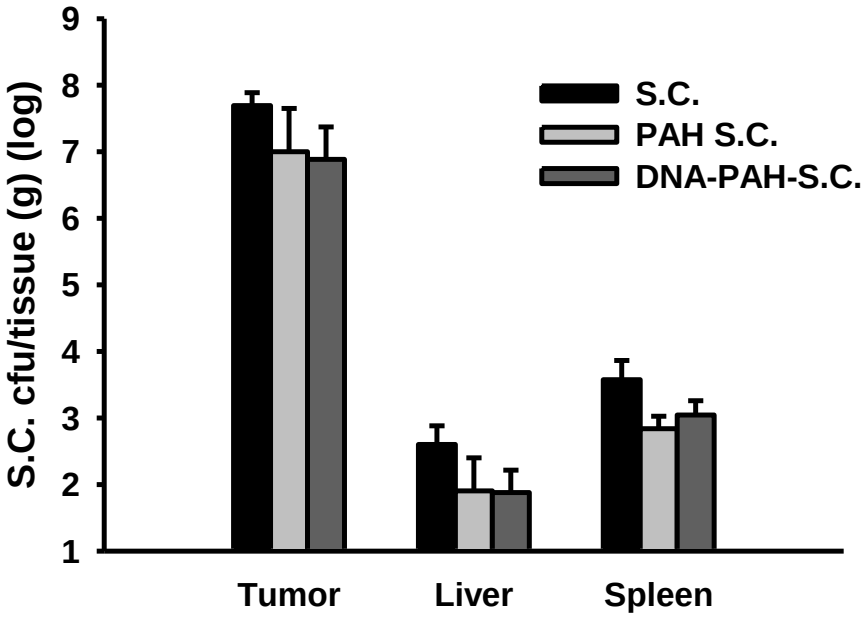
Polymers 6: 1119, 2014.

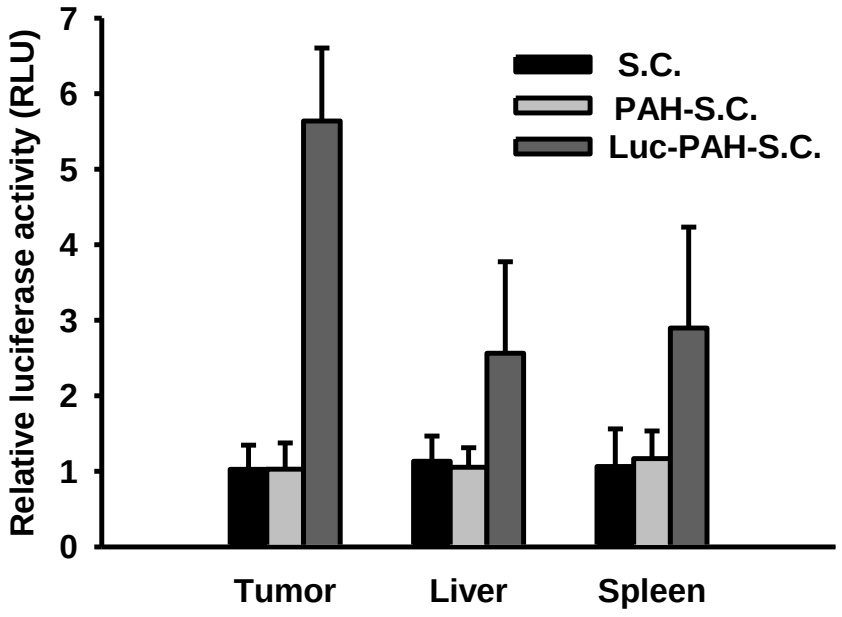
Transduction ability of DNA-PAH-*Salmonella*



Polymers 6: 119, 2014.

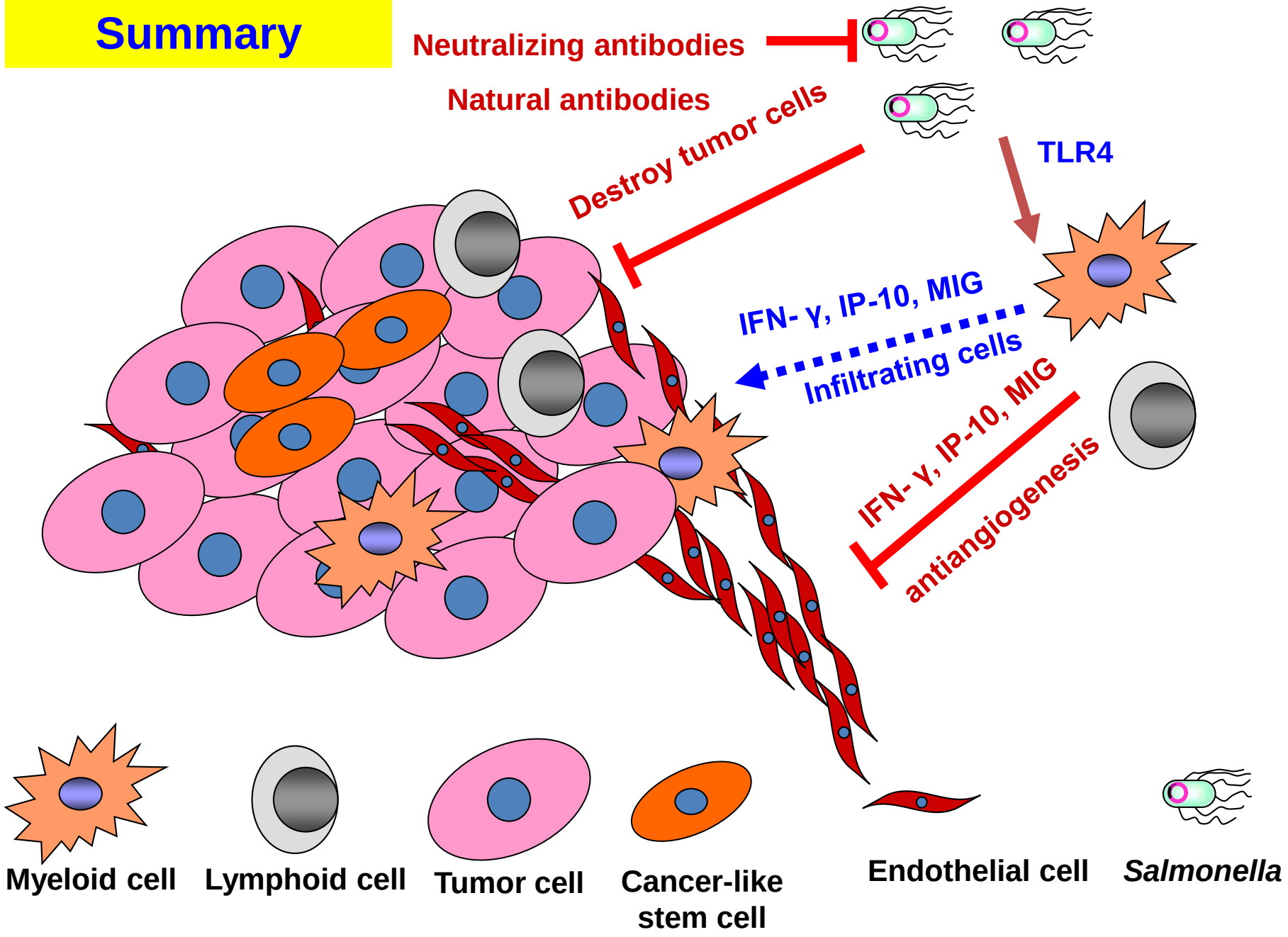
Tumor-targeting potential and gene transfer of DNA-PAH *Salmonella*





Polymers 6: 1119, 2014.

Summary


Neutralizing antibodies
Natural antibodies
Destroy tumor cells
TLR4
IFN- γ, IP-10, MIG
Infiltrating cells
IFN- γ, IP-10, MIG
antiangiogenesis
Myeloid cell
Lymphoid cell
Tumor cell
Cancer-like stem cell
Endothelial cell
Salmonella

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Thank you for your attention !