Taurolidine–a new drug with anti-tumor and anti-angiogenic effects

Christoph A. Jacobi[a], Charalambos Menenakos[a] and Chris Braumann[a,b]

Taurolidine [bis(1,1-dioxoperhydro-1,2,4-thiadiazinyl-4)-methane (TRD)], a product derived from the aminosulfoacid taurin, was first described as an anti-bacterial substance. It was mainly used in the treatment of patients with peritonis as well as antiendoxic agent in patients with systematic inflammatory response syndrome. Meanwhile, quite interesting new experimental findings elucidated several new mechanisms concerning not only antibiotic but also anti-tumor effects. TRD significantly reduces the pathogenicity of prokaryotes, leading to a degeneration of the bacterial wall, and binds free lipoplysaccharides (LPSs) and exotoxins. Furthermore syntheses of tumor necrosis factor-a and interleukin-1b are reduced in LPS-stimulated human macrophages in a dose dependent manner. Tumor angiogenesis is promoted by enhanced expression of all these endogenous angiogenic factors, indicating an anti-angiogenetic effect of TRD. Tumor angiogenesis has a key role in tumor growth. TRD additionally inhibits tumor cell growth by a mitochondrial cytochrome *c*-dependent apoptotic mechanism, has a direct and elective effect on glial and neuronal brain tumor cells via Fas-ligand-mediated cell death, and inhibits protein synthesis at an early phase of translation, which might explain its various apoptotic effects. Subsequent to these experimental observations, TRD has shown encouraging clinical results after intravenous administration in patients with gastrointestinal malignancies and tumors of the central nerve system. A remarkable experimental observation that comes to complete the above-mentioned findings is the low toxicity on leukopoiesis and erythropoiesis as well as on kidney and liver function in animal models. Several other data confirm low toxicity of the agent after its clinical administration in humans. Prospective clinical studies are currently investigating the efficacy of TRD on local and metastatic tumor growth in different malignancies. *Anti-Cancer Drugs* 16:917–921 © 2005 Lippincott Williams & Wilkins.

Anti-Cancer Drugs 2005, **16**:917–921

Keywords: anti-angiogenetic, anti-tumor, perspective, review, taurolidine, therapy

[a]Department of General, Visceral, Vascular and Thoracic Surgery and [b]Division of Molecular Biology, Medical Faculty Charité, Humboldt University, Berlin, Germany.

Correspondence to C. A. Jacobi, Department of General, Visceral, Vascular and Thoracic Surgery, Universitaetsmedizin Berlin, Charité Campus Mitte, Schumannstrasse 20/21, 10117 Berlin, Germany.
Tel: +49 30 450 522 031; fax: +49 30 450 522 932;
e-mail: christoph.jacobi@charite.de

Received 20 May 2005 **Accepted** 30 June 2005

Introduction

After i.p. and systemic application of taurolidine (TRD), a reduction of intra- and extraperitoneal metastases was observed in rats [1–3]. TRD seems to have a direct effect on tumor cells with a consecutive inhibition of cell growth [4–6]. Combined i.p. application of TRD and heparin showed synergic effects in some studies, so that their clinical use could be effective in the prevention of metastases in surgical oncology [7,8].

Prophylactic, intraoperative i.p. lavage with TRD for the prevention of metastatic disease has already been successfully applied. Intravenous application as a primary treatment of poorly managed malignancies is also considered and is currently being examined, as serious side-effects due to conventional chemotherapy could be prevented. Data from randomized prospective studies will expected in order to analyze its tumor-suppressing effects.

In addition to monotherapy with TRD, combined application of TRD as part of a therapy has been given great importance, so that synergic antineoplastic effects might be possible. In the following, we present some of the latest aspects of the antimicrobial and anti-tumorogenic effects of TRD, emphasizing the clinical implications.

Broad-spectrum antibiotic effects

TRD [bis(1,1-dioxoperhydro-1,2,4-thiadiazinyl-4)methane], a synthetic product derived from the aminosulfone acid taurin, consists of two aromatic rings (molecular weight 284.37), which are connected with a CH_2 group [5]. Hydrolysation divides the molecule in to taurultam (molecular weight 136.18) and methyl-taurultam. Both of them are active metabolites of TRD, which has been clinically used for many years in cases of peritonitis [9], according to its primary indication [10,11]. The i.p. and i.v. application showed only mild (vagotone) side-effects [12]. Reactive CH_2 groups bind on the bacterial wall, on receptors and on cell membranes. Thus, in contrast to other cytotoxic agents, TRD acts via a chemical reaction. Chemically reactive hydroxymethyl groups occupy binding sites in order to induce signals. The bacterial surface

0959-4973

(e.g. *Escherichia coli*, *Streptococcus pyogenes*) is damaged in only 5 min with a 2% TRD solution [10]. Cells lost their ability to undergo mitosis, and their pathogenetic and invasive features. In *Candida albicans*, adherence was reduced after a 30-min incubation with 0.05% (up to 0.125%) TRD in a time-dependent manner. Inhibitory concentrations of approximately 2 mg/ml have been observed. Later experiments showed that the hydroxymethyl groups react with the lipopolysaccharides (LPSs) of the endotoxins and the polypeptides of the exotoxins, diminishing their fatal consequences [13].

LPSs and exotoxins of bacterial pathogens possess a reaction potential that causes multiple functional disorders in several organs [14]. Chemical inactivation of toxins with TRD is partially based on the inter- and intramolecular connection of LPS protein complexes with CH_2 groups [10,14]. In several experiments, i.p. LPS was used to induce peritonitis in mice [15] and canine models. The toxicity was assessed according to alterations in body temperature and lethality. *In vitro* pre-incubation with TRD did not reduce the LPS toxicity. Administration of mice plasma, however, reduced the toxicity up to 25%. It seems that enzymatic processes are necessary for the *in vitro* transportation of the CH_2 groups. Several animal experiments confirmed these findings [2,16]. The effect of i.v. administered TRD on endotoxin levels in chronic inflammatory bowel disease was examined in rats [13]. Systematic toxicity was reduced compared to the control group (isotone saline solution, $P = 0.0008$). Similar results have been found in other experiments with bacterial peritonitis treated with TRD [4]. The local plasma endotoxin levels were lower compared to the control (saline). In BALB/c mice, translocation of bowel flora caused a local inflammatory reaction. Substances such as cytokines were released in that case. It is well known that TRD binds to the bacterial cell wall by cross-linking and therefore the release of LPS is prevented [10]. Therefore, the influence of the agent on cytokine levels was evaluated.

Reduction of interleukin (IL)-1, tumor necrosis factor (TNF)-α and vascular endothelial growth factor (VEGF)

The bacterial production of endotoxins (LPS) and exotoxins induces the release of several cytokines that can stimulate tumor growth [17]. It has been shown that TRD reduces the synthesis of TNF-α and IL-1β in LPS-stimulated human macrophages *in vitro* in a dose-dependent manner [18]. The cytokine levels decreased 80–90% after treatment with TRD (40–100 μg/ml) in vital cells. Additionally, the agent inhibited TNF-α production (and cell adhesion) in rat mesangioma cells [19]. In other experiments, the substance also reduced TNF-α production by malignant colonic tumor cells (DHD/K12/TRb) with an estimated IC_{50} value of 0.5 mmol/l. ELISA-based quantification of VEGF in the supernatants of the same cell line revealed that the production of the major pro-angiogenic factor was also reduced by a 6-h contact with TRD. The estimated IC_{50} value was 1.5 mM [20]. Furthermore, it has been shown that i.p. application of TRD decreased the local and serum levels of TNF-α in rats [21]. Thus, TRD might affect cytokine levels *in vitro* and *in vivo*. This effect was evaluated first on tumor growth *in vitro*.

Taurolidine reduces tumor growth *in vitro*

Previous cell kinetic experiments (96 h) have shown that TRD reduced tumor growth in human (CX 1) and rat colonic cells (DHD/K12/TRb) after a 2-h incubation *in vitro* [1]. This time is comparable to the abdominal administration used in the clinical setting. Although the applied concentrations *in vitro* were extremely low compared to clinical doses, a highly significant reduction in tumor growth was found during cell cycle periods. The results have been supported in other experiments [22]. TRD was also found to suppress the tumor growth of various cell lines [5]. Despite the fact that the concentrations described *in vitro* are more than 1000-fold lower compared to animal models, increasing doses led to a reduction of apoptosis (Table 1). TRD has been found to exert a direct and selective effect on glial and neuronal brain tumor cells via currently unknown apoptotic pathways [23]. The apoptotic effects were visualized by phosphatidyl externalization via Annexin-V assay. Concentrations between 50 and 100 μmol/l led to approximately 60–80% apoptosis. Nevertheless, the predominant data showed that TRD unselectively suppressed tumor cell growth *in vitro*. Recently, TRD has been shown to reduce proliferation rate, adhesion and migration of tumor cells in comparison to Ringer's solution [24]. TRD also reduces the bottom contact of tumor cells after a 72-h incubation (50–100 μmol/l) in an *in vitro* model [25]. Approximately 50–80% of melanoma cells lost their capacity to adhere. In human squamous cell carcinoma (SCC4 and SCC15) a 2-h treatment (0.01–0.5% TRD) significantly reduced cell proliferation and induced apoptosis [26]. The importance of adherence reduction of tumor cells has been described in different animal models.

Tumor growth inhibition in animal models

It is well known that intra-abdominal tumor cells can adhere, implant and grow in different anatomical sites [27]. Tumor cells will adhere more commonly on a damaged cell surface (intracellular substance) compared to an intact cell surface [28]. The most common trauma of mesothelial cells is made by the surgeon himself. Therefore, the influence of standardized mesothelial injuries on tumor growth (CC-531 cells) was analyzed in female WAG rats [29]. Three weeks after cell implantation, maximum tumor growth was found to correlate with the largest mesothelial lesions. In further experiments, tumor cells were implanted in kidneys. Mesothelial lesions were standardized and tumor growth was

Table 1 Tumor cell lines treated with different concentrations of TRD [the apoptotic impacts differ for the analyzed cell lines and correlate with the incubation time (e.g. PA-1)]

Reference	Cell lines	Tumor	Concentrations of TRD tested	Incubation time (h)	TRD concentration with the highest apoptotic effect
[39]	HL-60	leukemia	50–200 μmol/l	6	150 μmol/l
[23]	C6, HT22, U373	glioblastoma	3.5–14 mmol/l	6	35 μmol/l
[22]	HL-60	leukemia	1–10 mmol/l	1	1 mmol/l
	PA-1	ovarian	1–10 mmol/l	1	2.5 mmol/l
[5]	PA-1	ovarian	0.1–200 μmol/l	72	11.4 μmol/l
	SKOV-3	ovarian	0.1–200 μmol/l	72	31.6 μmol/l
	DU-145	prostate	0.1–200 μmol/l	72	9.8 μmol/l
	U-251	glioblastoma	0.1–200 μmol/l	72	20.1 μmol/l
	HT-29	colon	0.1–200 μmol/l	72	18.6 μmol/l
	HCT-8	colon	0.1–200 μmol/l	72	11.5 μmol/l
	HCT-15	colon	0.1–200 μmol/l	72	9.6 μmol/l
	B16-F10	melanoma	0.1–200 μmol/l	72	30.1 μmol/l
	MNT-1	melanoma	0.1–200 μmol/l	72	22.1 μmol/l
	H-157	lung	0.1–200 μmol/l	72	32.2 μmol/l
	A-549	lung	0.1–200 μmol/l	72	26.8 μmol/l
	H596	lung	0.1–200 μmol/l	72	34.2 μmol/l
[4]	DHD/K12/TRb	colon	18–88 μmol/l	24	18 μmol/l
[1]	DHD/K12/TRb, CX-1	colon	18–88 μmol/l	96	18 μmol/l
	HV1A3, TFK-1	gall bladder	18–88 μmol/l	96	18 μmol/l
	DHD/K12/TRb	colon	18–88 μmol/l	96	18 μmol/l
[25]	MNT-1	melanoma	12.5–100 μmol/l	72	25.4 μmol/l
	B16F10	melanoma	12.5–100 μmol/l	72	30.9 μmol/l
[26]	SCC 15	squamous cell	35–1.76 mmol/l	96	350 μmol/l
	SCC 4	squamous cell	35–1.76 mmol/l	96	1.76 mmol/l
[36]	REN, LRK, H28	malignant mesothelioma	0.1–200 μmol/l	24, 48 and 72	50, 100 and 150 μmol/l

evaluated, observing the same effects. The authors concluded that released cytokines induce adhesion molecules on the tumor cell surface. During the healing process, tumor cells were stimulated and levels of proteins such as lamin, fibronectin and vitronectin increased [30]. Heparin, a sulfated glycosaminoglycan, covalently binds receptors of the cellular surface and prevents adhesion of tumor cells [7,31]. Therefore, it was used in combination with other cytotoxic agents, such as TRD, to inhibit tumor growth in animals [2,32]. A single i.p. application of 1 ml 0.5% TRD (approximately 16 mM) significantly inhibited local tumor growth (DHD/K12/TRb, colon adenocarcinoma cells) in 210 BD-IX rats [3,8]. Neither i.p. reabsorption nor a single i.v. injection nor the combination of i.p. and i.v. application of the agents had any systemic anti-tumor effects. Preliminary data showed that 3% TRD reduces s.c. metastases weight and significantly inhibited tumor formation counts (DHD/K12/TRb) in BD-IX rats undergoing an 8-h injection for 1 week [12]. In ductal pancreatic cancer models, TRD was found to inhibit tumor growth and port site metastases [33,34]. The substance also effectively inhibited s.c. xenograft tumor growth (5×10^6 DU-145, human prostate cancer cell line) in male homozygous athymic mice (Hsd/athymic nude *nu*/*nu*) when applied i.p. [35]. Although tumor growth was effectively inhibited due to extremely high doses, the mortality rate was shown to be only 7%. In previous studies the i.p. use of the TRD reduced local tumor growth in rats undergoing laparotomy or laparoscopy [3,8]. New molecular mechanisms include inhibition of protein biosynthesis in eukaryotes, leading to cell death [20]. This action has not been observed in physiological tissue, which implies a selective effect on tumor cells and a lower toxicity.

The latest reports on the antitumor effects of TRD seem to be of great interest and are still promising. Kilian *et al.* reported a decreased number of liver metastases per animal and lower port site metastasis rate in hamsters with chemically induced ductal pancreatic cancer which had undergone TRD irrigation during laparoscopy [33]. Nici *et al.* reported a significant antineoplastic activity of TRD against malignant mesothelioma *in vitro* and *in vivo* [36]. In their experimental study, Volz *et al.* used 18 times lower doses of TRD compared to Braumann *et al.* [20], and showed a positive effect on survival in animals treated with TRD and pneumoperitoneum [37].

TRD was also found to inhibit the development of organ metastases (B16 melanoma cells), and to improve survival following laparoscopy and laparotomy in 540 mice [16].

Toxicity

A remarkable experimental observation is the low toxicity in leukopoiesis and lymphopoiesis in animal models. There was no difference in the perioperative course between long-term therapy and bolus treatment with TRD in rats compared to the control group which was treated with isotonic saline solution [38]. If these findings can be confirmed in human clinical studies, the low toxicity should be considered as a major advantage compared to the devastating toxicity of traditional chemotherapeutics. Currently studies in our

experimental laboratory aim to assess the toxicity on vital organs such as liver and kidneys. Results are eagerly awaited.

Taking all the data together, the combination of cytokine modulation and direct cytotoxicity seems to be responsible for the antitumor effects. The findings led to the i.p. and i.v. application of TRD in clinical trials.

Clinical use as an antitumor agent

The i.p. concentration of TRD used (0.5–*2%*) is extremely high when compared to doses applied *in vitro*. Both antiseptic and antitumor effects are expected, which make TRD very interesting for clinical use. In a prospective randomized multicenter trial the effects on cytokine release (IL-1β) of i.p. 0.25% povidone iodine versus 0.5% TRD were analyzed in 120 patients (own unpublished data, conventional resections of colon cancer $n = 57$, gastric cancer $n = 52$ and pancreatic malignancies $n = 11$). The cytokines IL-6, IL-10 and TNF-α (serum and i.p. levels) as well as the incidence of local recurrences or metastases were examined. Randomized patients were i.p. treated with TRD (0.5%) Ringer's solution and 0.25% povidone iodine (control) at the beginning of the operation and after tumor resection. No clinically relevant side-effects were observed during administration or after reabsorption. The data on the cytokine levels, local recurrences, metastases and mortality rate are expected at the end of 2005. A new study (phase III) examined the influence of an i.v. therapy (*2%* TRD, 300 mg/kg body weight/day) on gastric and pancreatic cancer recurrence ($n = 50$). The monthly repeated 7-day treatment sessions were performed using a central vein port catheter and a pump perfusor system. No clinically relevant side-effects were seen in the first 15 patients. Additionally, quality of life, response rate and mortality rate were evaluated under a standardized protocol. So far, reduced tumor markers at the end of a 7-day therapy have been observed in most patients. Stable disease was observed in three cases (gastric cancer recurrence group). One patient submitted to the 38th chemotherapy session without any tumor progress with a good quality of life. Reviewing the literature, it seems that the drug is effective on several tumor cell lines. Two patients with malignant glioblastoma were i.v. treated (*2%* TRD 1000 ml = 20 g/day). Although both patients died 4 months later (acute thromboembolism and pneumonia), a transient improvement in quality of life and a partial tumor remission were observed [6]. A clear response on the TRD treatment was seen in the computed tomography scan. The underlying pathological mechanisms are still under investigation.

Pathological mechanisms responsible for antitumor effects

TRD has two ringed molecules linked by a methylene bridge. In water, the drug is in equilibrium with taurultam and methylol-taurultam hydrolysed to two molecules of taurultam. The latter is further biotransformed to methylol-taurinamide → taurinamide → taurine → CO_2. The approximately half-lives of taurultam are $t_{1/2(\alpha)} = 0.75$ h and $t_{1/2(\beta)} = 6.7$ h after i.p. application. The half-lives after i.v. injection are $t_{1/2(\alpha)} = 0.14$ h and $t_{1/2(\beta)} = 2.2$ h [10]. TRD was first described as an antibacterial agent and used in the treatment of peritonitis or in patients with systemic inflammatory response syndrome [9]. It has been hypothesized that the suppression of tumor growth may be explained by intracellular effects leading to apoptosis, presumably by a mitochondrial cytochrome *c*-dependent apoptotic mechanism [39] or by a caspase-dependent pathway [36]. Lately, the agent has been found to exert a direct, selective effect on glial and neuronal brain tumor cells via Fas ligand-mediated cell death [40]. TRD decreases TNF-α and IL-1β production in peritoneal macrophages, which might explain the additional anti-tumor effect on local cell growth [41]. TNF-α secreted by macrophages stimulates tumor angiogenesis, presumably by activating the major pro-angiogenic factor VEGF in tumor cells. Additionally, TNF-α is known to down-regulate apoptosis by activation of NF-κB, an important transcription factor [42]. More recently, it was shown that TRD acts as an inhibitor of an early phase in translation [20]. Transcription and translation processes were performed in separate steps. Transcription of c-Jun cDNA in the presence of 16 mM TRD (0.5%) revealed no effect on the process. In contrast, translation of c-Jun mRNA was completely blocked by TRD. Different phases of translation, such as formation of the initiation complex, of the functional 80S ribosome and of polysomes, were separated by density gradient centrifugation and visualized using [^{32}P]mRNA. It could be demonstrated that TRD affects translation at a very early stage. It seems that no pre-initiation complex was formed. In the presence of TRD, protein biosynthesis was blocked in mammalian cells as well as in bacteria, which might explain most of its effects, including induction of apoptosis.

Conclusion and perspectives

TRD prevents growth and spread of tumor cells, reduces levels of cytokines as well as the major pro-angiogenic factor VEGF, and also acts as an antibacterial agent. The use of TRD as an i.p. instillation after surgical resection of abdominal malignancies has advantages based on its different effects and as an inductor of apoptosis. So far, no clinically relevant side-effects have been observed when an i.p. or i.v. maximum concentration of 300 mg/kg body weight/day was administered. Clinical use will be analyzed in prospective studies in humans in order to determine the efficacy on local and metastatic tumor growth on different malignancies. Standardized clinical protocols for i.p. and i.v. therapy are necessary to examine

TRD's toxicity and effectiveness in the multidisciplinary treatment of malignancies.

Acknowledgement

We thank Professor Dr J. M. Mueller, Director of the Department of Surgery, and Professor Dr W. Dubiel, Chief of the Division of Molecular Biology, for continuous support.

References

1 Jacobi CA, Peter FJ, Wenger FA, Ordemann J, Muller JM. New therapeutic strategies to avoid intra- and extraperitoneal metastases during laparoscopy: results of a tumor model in the rat. *Dig Surg* 1999; **16**:393–399.
2 Jacobi CA, Ordemann J, Bohm B, Zieren HU, Sabat R, Muller JM. Inhibition of peritoneal tumor cell growth and implantation in laparoscopic surgery in a rat model. *Am J Surg* 1997; **174**:359–363.
3 Braumann C, Ordemann J, Wildbrett P, Jacobi CA. Influence of intraperitoneal and systemic application of taurolidine and taurolidine/heparin during laparoscopy on intraperitoneal and subcutaneous tumor growth in rats. *Clin Exp Metastasis* 2000; **18**:547–552.
4 McCourt M, Wang JH, Sookhai S, Redmond HP. Taurolidine inhibits tumor cell growth *in vitro* and *in vivo*. *Ann Surg Oncol* 2000; **7**:685–691.
5 Calabresi P, Goulette FA, Darnowski JW. Taurolidine: cytotoxic and mechanistic evaluation of a novel antineoplastic agent. *Cancer Res* 2001; **61**:6816–6821.
6 Da Costa ML, Redmond HP, Bouchier-Hayes DJ. Taurolidine improves survival by abrogating the accelerated development and proliferation of solid tumors and development of organ metastases from circulating tumor cells released following surgery. *J Surg Res* 2001; **101**:111–119.
7 Gill WB, Jones KW, Ruggiero KJ. Protective effects of heparin and other sulfated glycosaminoglycans on crystal adhesion to injured urothelium. *J Urol* 1982; **127**:152–154.
8 Braumann C, Ordemann J, Kilian M, Wenger FA, Jacobi CA. Local and systemic chemotherapy with taurolidine and taurolidine/heparin in colon cancer-bearing rats undergoing laparotomy. *Clin Exp Metastasis* 2003; **20**:387–394.
9 Billing A, Frohlich D, Ruckdeschel G. [The effect of taurolin on endogenous immunity and pathogen elimination in human peritonitis]. *Langenbecks Arch Chir* 1992; **377**:180–185.
10 Pfirrmann RW. Taurolin in der Anwendung bei chirurgischen Infektionen. *Chir Gastroenterol* 1991; **6**:131–142.
11 Staubach KH. [Adjuvant therapy of peritonitis with taurolidine. Modulation of mediator liberation]. *Langenbecks Arch Chir* 1997; **382**:S26–S30.
12 Braumann C, Stuhldreier B, Bobrich E, Menenakos C, Rogalla S, Jacobi CA. High doses of taurolidine inhibit advanced intraperitoneal tumor growth in rats. *J Surg Res* 2005; in press.
13 Gardiner KR, Anderson NH, McCaigue MD, Erwin PJ, Halliday MI, *et al.* Enteral and parenteral anti-endotoxin treatment in experimental colitis. *Hepatogastroenterology* 1994; **41**:554–558.
14 Dofferhoff AS, Esselink MT, Vries-Hospers HG, van Zanten A, Bom VJ, Weits J, *et al.* The release of endotoxin from antibiotic-treated *Escherichia coli* and the production of tumor necrosis factor by human monocytes. *J Antimicrob Chemother* 1993; **31**:373–384.
15 Pidgeon GP, Harmey JH, Kay E, Da Costa M, Redmond HP, Bouchier-Hayes DJ. The role of endotoxin/lipopolysaccharide in surgically induced tumor growth in a murine model of metastatic disease. *Br J Cancer* 1999; **81**: 1311–1317.
16 Darnowski JW, Goulette FA, Cousens LP, Chatterjee D, Calabresi P. Mechanistic and antineoplastic evaluation of taurolidine in the DU145 model of human prostate cancer. *Cancer Chemother Pharmacol* 2004; **54**:249–258.
17 Watson RW, Redmond HP, McCarthy J, Bouchier-Hayes D. Taurolidine, an antilipopolysaccharide agent, has immunoregulatory properties that are mediated by the amino acid taurine. *J Leukoc Biol* 1995; **58**:299–306.
18 Lanfrancone L, Boraschi D, Ghiara P, Falini B, Grignani F, Peri G, *et al.* Human peritoneal mesothelial cells produce many cytokines (granulocyte colony-stimulating factor CSF), granulocyte-monocyte-CSF, macrophage-CSF, interleukin-1 IL-1], and IL-6) and are activated and stimulated to grow by IL-1. *Blood* 1992; **80**:2835–2842.
19 Leithauser ML, Rob PM, Sack K. Pentoxifylline, cyclosporine A and taurolidine inhibit endotoxin-stimulated tumor necrosis factor-alpha production in rat mesangial cell cultures. *Exp Nephrol* 1997; **5**:100–104.
20 Braumann C, Henke W, Jacobi CA, Dubiel W. The tumor-suppressive reagent taurolidine is an inhibitor of protein biosynthesis. *Int J Cancer* 2004; **112**:225–230.
21 Rosman C, Westerveld GJ, van Oeveren W, Kooi K, Bleichrodt RP. Effect of intraperitoneal antimicrobials on the concentration of bacteria, endotoxin, and tumor necrosis factor in abdominal fluid and plasma in rats. *Eur Surg Res* 1996; **28**:351–360.
22 Ribizzi I, Darnowski JW, Goulette FA, Akhtar MS, Chatterjee D, Calabresi P. Taurolidine: preclinical evaluation of a novel, highly selective, agent for bone marrow purging. *Bone Marrow Transplant* 2002; **29**:313–319.
23 Stendel R, Stoltenburg-Didinger G, Al Keikh CL, Wattrodt M, Brock M. The effect of taurolidine on brain tumor cells. *Anticancer Res* 2002; **22**:809–814.
24 Nestler G, Schulz HU, Schubert D, Kruger S, Lippert H, Pross M. Impact of taurolidine on the growth of CC531 colon carcinoma cells *in vitro* and in a laparoscopic animal model in rats. *Surg Endosc* 2005; **19**:280–284.
25 Shrayer DP, Lukoff H, King T, Calabresi P. The effect of Taurolidine on adherent and floating subpopulations of melanoma cells. *Anticancer Drugs* 2003; **14**:295–303.
26 Petrovic L, Schlegel KA, Ries J, Park J, Diebel E, Schultze-Mosgau S, *et al.* [*In vitro* effect of taurolidine on squamous cell carcinoma in the oral cavity]. *Mund Kiefer Gesichtschir* 2003; **7**:102–107.
27 Lee SW, Whelan RL, Southall JC, Bessler M. Abdominal wound tumor recurrence after open and laparoscopic-assisted splenectomy in a murine model. *Dis Colon Rectum* 1998; **41**:824–831.
28 Fisher B, Fisher ER, Feduska N. Trauma and the localization of tumor cells. *Cancer* 1967; **20**:23–30.
29 Tol PM, van Rossen EE, van Eijck CH, Bonthuis F, Marquet RL, Jeekel H. Reduction of peritoneal trauma by using nonsurgical gauze leads to less implantation metastasis of spilled tumor cells. *Ann Surg* 1998; **227**:242–248.
30 Ruoslahti E, Pierschbacher MD. New perspectives in cell adhesion: RGD and integrins. *Science* 1987; **238**:491–497.
31 Solberg R, Scholz T, Videm V, Okkenhaug C, Aasen AO. Heparin coating reduces cell activation and mediator release in an *in vitro* venovenous bypass model for liver transplantation. *Transplant Int* 1998; **11**:252–258.
32 Opitz I, van der Veen HC, Braumann C, Ablassmaier B, Fuhrer K, Jacobi CA. The influence of adhesion prophylactic substances and taurolidine/heparin on local recurrence and intraperitoneal tumor growth after laparoscopic-assisted bowel resection of colon carcinoma in a rat model. *Surg Endosc* 2003; **17**:1098–1104.
33 Kilian M, Gregor JI, Heukamp I, Braumann C, Guski H, Schimke I, *et al.* Impact of taurolidin and octreotide on liver metastasis and lipid peroxidation after laparoscopy in chemical induced ductal pancreatic cancer. *Invest New Drugs* 2005; **23**:157–164.
34 Kilian M, Mautsch I, Braumann C, Schimke I, Guski H, Jacobi CA, *et al.* Effects of taurolidine and octreotide on tumor growth and lipid peroxidation after staging-laparoscopy in ductal pancreatic cancer. *Prostaglandins Leukot Essent Fatty Acids* 2003; **69**:261–267.
35 Wenger FA, Kilian M, Braumann C, Neumann A, Ridders J, Peter FJ, *et al.* Effects of taurolidine and octreotide on port site and liver metastasis after laparoscopy in an animal model of pancreatic cancer. *Clin Exp Metastasis* 2002; **19**:169–173.
36 Nici L, Monfils B, Calabresi P. The effects of taurolidine, a novel antineoplastic agent, on human malignant mesothelioma. *Clin Cancer Res* 2004; **10**:7655–7661.
37 Volz J, Volz-Koster S, Kanis S, Klee D, Ahlert C, Melchert F. Modulation of tumor–induced lethality after pneumoperitoneum in a mouse model. *Cancer* 2000; **89**:262–266.
38 Braumann C, Schoenbeck M, Menenakos C, Kilian M, Jacobi CA. Effects of increasing doses of a bolus injection and an intravenous long term therapy of taurolidine on subcutaneous (metastatic) tumor growth in rats. *Clin Exp Metastasis* 2005; **22**:77–83.
39 Han Z, Ribbizi I, Pantazis P, Wyche J, Darnowski J, Calabresi P. The antibacterial drug taurolidine induces apoptosis by a mitochondrial cytochrome *c*-dependent mechanism. *Anticancer Res* 2002; **22**:1959–1964.
40 Stendel R, Scheurer L, Stoltenburg-Didinger G, Brock M, Mohler H. Enhancement of Fas-ligand-mediated programmed cell death by taurolidine. *Anticancer Res* 2003; **23**:2309–2314.
41 Torisu H, Ono M, Kiryu H, Furue M, Ohmoto Y, Nakayama J, *et al.* Macrophage infiltration correlates with tumor stage and angiogenesis in human malignant melanoma: possible involvement of TNFalpha and IL-1alpha. *Int J Cancer* 2000; **85**:182–188.
42 Van Antwerp DJ, Martin SJ, Verma IM, Green DR. Inhibition of TNF-induced apoptosis by NF-kappa B. *Trends Cell Biol* 1998; **8**:107–111.