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Review

Bioprofiling TS/A Murine Mammary Cancer for a Functional Precision Experimental Model

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Abstract: The TS/A cell line was established in 1983 from a spontaneous mammary tumor arisen in an inbred BALB/c female mouse. Its features (heterogeneity, low immunogenicity and metastatic ability) rendered the TS/A cell line suitable as a preclinical model for studies on tumor–host interactions and for gene therapy approaches. The integrated biological profile of TS/A resulting from the review of the literature could be a path towards the description of a precision experimental model of mammary cancer.

Keywords: TS/A; murine mammary cancer; preclinical models; gene therapy; metastases; immunotherapy

1. Introduction

Precision medicine in clinics is an evolving concept which goes beyond mere genomic medicine and means matching individual patients with medicine [1]. According to these premises, in an experimental environment a precision cancer model should mean matching the appropriate preclinical model with target biology study [2]. Preclinical models of mammary cancer of increasing complexity have been proposed, including transplantable murine tumors, gene-driven mammary carcinogenic models, human cell lines grown in vitro or in vivo as xenografts and patient-derived xenografts and organoids (see Section 6 for a comparative discussion) [3,4]. Each model remains an approximation [2], with advantages and disadvantages depending on the specific aim of the study. The main advantage of transplantable murine mammary tumors consists of allowing mechanistic studies on tumor–host interactions, like those focusing on the role of microenvironment, the metastatic process and the immune response. A deep knowledge of a preclinical model, where literature studies are collected and retrospectively examined as a whole, like an individual patient's medical record, can help in a better design of experimental approaches. The aim of this review is the biological profiling of a popular model of murine mammary cancer (TS/A) for a better understanding and modeling of a complex pathology like human breast cancer [5].

2. The Dawn of Murine Models for Tumor–Host Interactions

At the beginning of the 1980s, metastases and tumor–host interaction studies mostly took advantage of a few tumor cell lines, established and subcultured for many years, such as 3LL Lewis lung carcinoma and B16 murine spontaneous melanoma [6]. Through the intravenous injection of

B16 cells, metastatic deposits to lungs and other organs could be easily obtained, allowing for important advancements in understanding post-intravasation late phases of the metastatic process. However, the B16 parental cell line was almost incapable of disseminating from a locally-growing tumor, and therefore it did not adequately model the invasion and intravasation phases. Moreover, the non-epithelial origin of B16 melanoma impeded inferences about the behavior of epithelial tumors. At the same time, some rodent cell lines were already being used as models for mammary cancer, but most of them were either carcinogen- or virus-induced [7,8]. These models did not undergo a long natural history in the host, in which they arose, and generally had a high immunogenicity due to the expression of strong tumor-associated antigens. Likely due to these features, they generally gave too optimistic results when used to study antitumor immune responses or immunotherapeutic approaches [9].

In this landscape, in 1983 we described a new cell line, TS/A, derived from a mammary tumor spontaneously arisen in a 20 month-old BALB/c inbred mouse strain [10]. The TS/A cell line exhibited some features typical of human breast cancer, which prompted its use as a preclinical model, such as the low immunogenicity, the ability of local tumors to give rise to distant metastases and the heterogeneity, well evident both of morphology and metastatic ability. The TS/A cell line (also referred to as TSA or TS/A-pc, see [11,12] and below) and its clones were distributed to many laboratories worldwide and were employed for different applications, such as studies on malignant phenotype, pharmacologic therapeutic approaches, antitumor immune response and as a gene therapy model.

A list of research studies exploiting the TS/A cell line or its cell variants is reported in the Supplementary Table S1. It includes (up to 2018) 276 research papers where TS/A was used as model system and 19 papers where it was a control model. Reviews reporting results obtained with TS/A and citations of the TS/A paper are also listed in the Supplementary Table S1.

This review aims at profiling the main biological features of the TS/A model system resulting from literature research papers (Table 1). The two research areas where TS/A-based models yielded important results will be discussed in depth: tumor–host interactions and experimental gene therapy.

Table 1. TS/A model: main features.

Topics	Cell variants	Features	Refs
Cytoskeletal markers	E1	CK8-positive	[13]
Cytokine production	TS/A, clones and variants	CSF	[14–17]
	TS/A	TGF-β1 production (about 4 ng/mL)	[18]
Cytokine receptors	TS/A	IFN-γ receptor (1000/cell)	[19]
Gene alterations	TS/A	Karyotype	[20]
	TS/A and E1	p53 mutated (codon 270 Arg to His)	[13,21]
Gene expression	TS/A	TERT (11,000 RNA copies)	[22]
Hormone sensitivity	TS/A and E1	Estrogen receptor positive	[10,13]
Immunity	TS/A	Low immunogenicity	[10,23,24]
	TS/A and engineered variants	Tumor associated antigen gp70env	[25]
	TS/A	Suppressor activity	[26,27]
	TS/A	Myeloid-derived suppressor cells (MDSC)	[28–35]
	TS/A	NK resistance	[36]
	TS/A	mD52 antigen	[37]
Membrane molecules	TS/A	Core 1 O-glycans	[38]
	TS/A	Muc-1	[39]
	TS/A	Tag72	[39]
Phenotype	TS/A, clones and variants	Heterogeneity (morphology, metastasis)	[10,40,41]
Stem cell markers	TS/A	Sca-1 (Ly6A/E)	[42,43]

Tyrosine Kinase membrane receptors	TS/A	p185erbB2	[39,44]
Others	TS/A	Endoglin-negative	[45]
	TS/A	Fragile X mental retardation protein (FMRP), low expression	[46]
	TS/A	High Mobility Group Box1 (HMGB1)-positive	[47]
	TS/A	Lats2	[48]
	TS/A	ST6Gal activity (present, low)	[49]
	TS/A	TLR9-negative	[50]

3. Bioprofiling TS/A Cell Line

The mammary tumor originating the TS/A cell line was isolated in a 20 months-old BALB/c female retired breeder and was described as a moderately differentiated adenocarcinoma [10]. Its first in vivo passage into a healthy BALB/c female was adapted to in vitro culture and named TS/A (Figure 1). Several clones and cell variants were derived from TS/A and distributed worldwide. In particular, a TS/A subline was chosen by Guido Forni (University of Turin) for a large collaborative endeavor as the recipient cell for the systematic transduction of a large series of genes coding for immune modulators; such subline was referred to as TS/A-pc (from "parental cells"). TS/A and TS/A-pc share most features reviewed here, and some kind of drift occurred during the extensive amplification of TS/A-pc. Throughout this review, we will refer to the TS/A model system on the whole, and therefore incorrect terminology (such as TSA, TS/a, and so on) has been systematically corrected to "TS/A". However, the Supplementary Table reports exactly the TS/A cell variant used in each referenced paper.

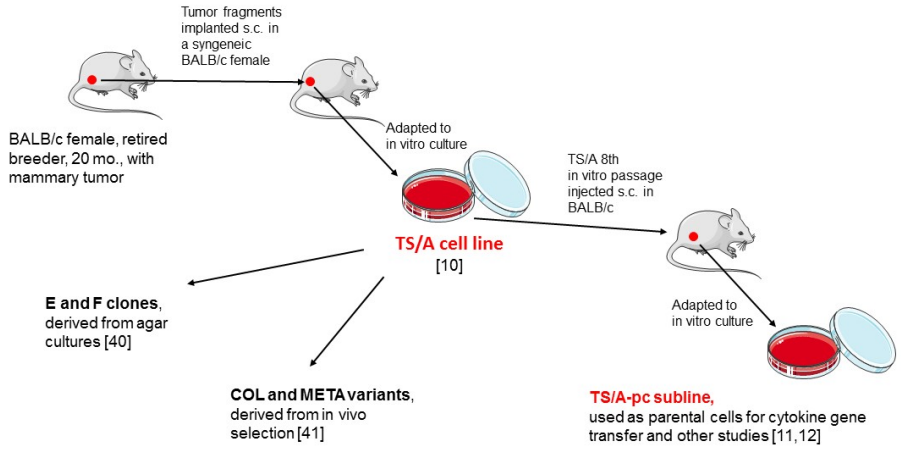

Figure 1. Origin of the TS/A cell line and variants. For pictures see [51].

The tumor from which the TS/A cell line was derived likely had a long natural history in its host of origin. When tested in a growth-excision test, TS/A cells did not confer protection against a second challenge, thus showing a low immunogenicity [10], thereafter confirmed in other studies (see, for example, [23]). Such a low immunogenicity was the basis for a huge number of immunopotentiation studies, most of which exploiting gene therapy approaches (see next section).

TS/A cells express the gp70env product of an endogenous retrovirus whose AH1 immunodominant class I epitope could be recognized by cytotoxic T lymphocytes through presentation by H-2L^d [25]. Gp70env antigen is shared by other murine cell lines, such as the colorectal cancer cell line CT26. The down-regulation of the L^d observed in TS/A cells [52] is likely due to the immunoediting process leading to evasion from the host immune response.

TS/A exerts a suppressive effect on the host immune response through several mechanisms, such as a selective loss of STAT5a/b expression in T and B lymphocytes [26], the production of

transforming growth factor β1 (TGF-β1) [18], the induction of regulatory T cells [27], natural killer resistance [36] and the production of colony stimulating factors (CSFs) that deeply subvert hematopoiesis [14,15], giving rise to splenomegaly, leucocytosis and to tumor-infiltrating myeloid-derived suppressor cells (MDSC) [29,33,53].

When injected subcutaneously into syngeneic BALB/c mice, TS/A cells gave rise to local tumors rapidly disseminating to the lungs. Metastases could also be obtained after injection of TS/A cells by the intravenous route, thus allowing a comparison between the dynamics of the early and late phases of the metastatic process [10,41]. Metastases to lungs and liver have also been obtained by orthotopic cell injection [54]. Like other mammary carcinoma cell lines, the growth of micrometastases at distant organs was found to involve the formation of filopodium-like protrusions mediated by FAK/ERK and Rif/mDia2 signaling [54].

Heterogeneity of TS/A cells was observed in adherent cultures, with areas of epithelial-like and fibroblast-like morphology (Figure 2), and in anchorage-independent cultures [10,40]. Subcloning from agar cultures allowed the isolation of two types of cell clones, both tumorigenic and metastatic, but with markedly different metastatic power [40]. Unexpectedly high-metastatic clones had a prevalent epithelial morphology, compared to the fibroblast-like pattern of low-metastatic clones. Gene expression profiling of several murine mammary cancer cell lines showed clustering of TS/A-E1 (a high-metastatic clone) with high-claudin expressors [13]. Our data on gene expression profiling of TS/A clones showed that claudin-3 was the top overexpressed gene in high-metastatic clones (about 90-fold expression over low-metastatic clones), while low-metastatic clones overexpressed nme4 and necdin, two putative metastasis suppressor genes (our unpublished results). These data suggest that metastatic ability is not always a consequence of epithelial–mesenchymal transition but can also be acquired in an epithelial-like differentiation context.

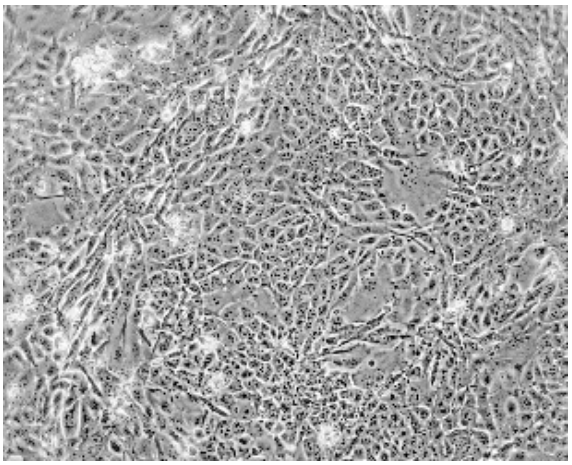

Figure 2. Morphology of the TS/A cell line in adherent culture (phase contrast, ×100).

The TS/A cell line has a triploid karyotype [20] and carries a mutated p53 at codon 270 [21]. About a third of the cells express the cancer stem cell marker Sca-1 [43]. In our laboratory, the expression of Sca-1 (also known as Ly6A) was almost negative, but inducible by IFN-γ [12]. TS/A cells express estrogen receptor [10] and endogenous murine p185-erbB2 product [39]. Its use as a negative HER2/neu mammary cancer cell line in studies on HER2/neu transgenic models relies upon the negativity to the reagent specifically recognizing rat HER2/neu.

4. Tumor–Host Interaction Studies

TS/A-induced tumors have a rich and heterogeneous infiltrate comprising granulocyte and monocyte/macrophage subpopulations, whose relative proportions change during tumor progression [55], in agreement with the known plasticity of myeloid cells. Several subpopulations contribute to maintainance of a tumor-promoting microenvironment in TS/A, as well as in many

other murine and human tumors [56], with a variety of mechanisms. Alternatively-activated M2 macrophages are strong producer of the immunosuppressive cytokine IL10 and of several chemokines recruiting Treg, Th2, eosinophils and basophils [56]. MDSC are heterogeneous immature CD11b+/Gr-1+ populations [57], with immunosuppressive function. Both M2-polarized macrophages and MDSC have been investigated in the TS/A model system, along with strategies to circumvent tumor promotion, pushing infiltrate cells towards more differentiated, activated cells.

In the TS/A model, the induction of M2 tumor-associated macrophages was mediated by the expression of the CD20 homolog *MS4A8A* gene [58]. In TS/A tumors, M2-polarized macrophages were more abundant and more proangiogenic in hypoxic tumor areas [55]. The M2 immune suppressing phenotype was switched to an anti-tumor M1 phenotype through the in vivo adenoviral gene transfer of the chemokine CCL16 [59]. Alternatively-activated M2 macrophages expressed highly restricted, individual-specific, combinatorial T cell receptor-αβ immunoreceptors, suggestive of an adaptive response of macrophages to the tumor [60]. In TS/A, as well as in a variety of other murine and human tumors, alternatively-activated M2 tumor-associated macrophages expressed a multifunctional scavenger receptor named stabilin-1 involved in endocytic and phagocytic clearance of "unwanted-self" components, including soluble component of extracellular matrix SPARC (a tumor-inhibiting agent). Stabilin-1 was found to play a tumor promoting role in the TS/A model likely through enhanced clearance of SPARC [61].

A major component of TS/A infiltrate consisted of MDSC [53], which correlated with the production of CSFs by TS/A cells [14,29]. Immature myeloid progenitors can be released in the bloodstream, giving rise to peripheral leukocytosis and splenomegaly [14,15]. MDSC suppressed antigen-activated T lymphocytes through apoptosis induction [28,29], and suppressed NK cytotoxicity [62], with mechanisms involving nitric oxide [30]. Impaired anti-tumor immune response in aging can take advantage of an increased MDSC infiltrate [32]. MDSC expressed Fas–FasL and caspases, suggesting that Fas–FasL apoptosis regulated MDSC survival [33,34] and proposing new potential therapeutic options. MDSCs are key drivers of resistance to antiangiogenic therapy, but all-trans retinoic acid was able to induce differentiation of MDSC into mature cells, thus increasing the efficacy of the antiangiogenic therapy [63].

In the TS/A microenvironment, other non-tumoral cell types can play a tumor-promoting role, such as tumor-associated fibroblasts and adipocytes. Through a tumor-stromal cell co-injection model, novel candidate tumor-associated genes were identified in tumor-associated fibroblasts. The most studied gene was tubulin tyrosine ligase: its downregulation in tumor-associated fibroblasts promoted TS/A tumor growth [64]. Co-culture of TS/A cells with adipocytes caused an increased lipid content in TS/A cells and an increased lung colonization ability [65]. The release of free fatty acids from lipid droplets is mediated by an adipose triglyceride lipase-dependent lipolytic pathway, that was proposed as a potential therapeutic target. The metabolic cross-talk between tumor cells and tumor-associated adipocytes could favor epithelial-mesenchymal transition and increase tumor invasiveness.

TS/A cells, like other tumor cell lines, secrete membrane vesicles of endosomal origin called "exosomes", with contradictory roles in tumor biology. Exosomes could have some immunostimulatory effect, since they carry tumor antigens which can be transferred to dendritic cells and cross-prime cytotoxic T lymphocytes [66]. However, exosomes mainly exerted a potent immunosuppressive anti-tumor immune response through suppression of NK cell function [67] and inhibition of differentiation of bone marrow dendritic cells [68]. Tumor-derived exosomes released from irradiated TS/A cells showed an altered molecular composition and were able to transfer dsDNA to dendritic cells and stimulate upregulation of costimulatory molecules and STING-dependent activation of IFN-I [69].

5. Gene Therapy Studies

TS/A cells were easily transduced both with naked DNA and viral systems, generating good and stable transgene expression of secreted factors or membrane molecules. Most gene therapy

approaches were performed to directly increase TS/A immunogenicity with the purpose to use engineered cells as anticancer vaccines (Table 2).

Table 2. TS/A in gene therapy studies aiming to increase tumor immunogenicity.

Immune categories	Transgenes	Vector/transfer methods	Refs
Chemokines	h-CCL16/LEC	Naked DNA + lipofection	[70,71]
		Adenoviral, in vivo	[59,72]
Cytokines	m-IL2	Naked DNA + electroporation	[11,23,73–77]
	m-IL4	Retroviral	[73,74,78–85]
	m-IL5	Retroviral	[86,87]
	m-IL6	Retroviral	[74,80,87]
	m-IL7	Naked DNA + electroporation	[73,74,80,81,88,89]
	m-IL7	Adenoviral	[90]
	m-IL10	Naked DNA + electroporation	[74,91]
	m-IL12 p35 and p40	Naked DNA, in vivo	[92,93]
		Naked DNA + gene gun	[94]
		Naked DNA + lipofection	[95]
		Retroviral	[96,97]
		Canarypox	[98]
		Naked DNA + gene gun, in vivo	[24]
	h-IL13	Naked DNA + calcium phosphate	[99]
	m-IL15	Adenoviral	[100]
	IL15	Naked DNA + lipofection	[95,101]
	Pro-IL18 and ICE	Naked DNA + gene gun	[94]
	m-IL21	Naked DNA + lipofection	[102]
	m-IFNα1	Naked DNA + electroporation	[80,82,103–106]
	m-IFNα1	Naked DNA + gene gun	[107]
	m-IFNα4	Naked DNA + polymer	[108]
	m-IFNβ	Naked DNA + calcium phosphate	[109]
	m-IFNγ	Naked DNA + lipofection	[12,74,80,99,110–113]
	m-GMCSF	Retroviral	[74]
	m-TNFα	Retroviral	[74,80]
Membrane molecules	B7-1/CD80	Naked DNA	[114]
		Naked DNA + electroporation	[115,116]
		Retroviral	[81,89]
	B7-2/CD86	Naked DNA + electroporation	[115,116]
	Allogeneic MHC	Naked DNA + calcium phosphate	[111,117]
	CD70 (CD27L)	Retroviral	[118,119]
	CD153 (CD30L)	Retroviral	[118]
	CD154 (CD40L)	Retroviral	[118,120]
	TRAIL/APO2L	Naked DNA + lipofection	[121]
	LAG-3 and LAG5	Naked DNA + electroporation	[122,123]
	CCR7	Naked DNA + calcium phosphate	[124]
Suicide genes	Cytosine deaminase	Retroviral	[112,125]
		Naked DNA	[126]
		VSV (oncolytic)	[127,128]
	HSV-Thymidine kinase	Naked DNA	[104]
		Retroviral	[129]
		Naked DNA + lipofection	[130]
Others	CIITA	Naked DNA + lipofection	[131–133]
	GBP1	Retroviral (conditional) + naked DNA	[134]
	m-IRF1	Adenoviral	[135]

Genes for a variety of cytokines, costimulatory molecules and major histocompatibility complex (MHC) antigens were inserted and stably expressed in TS/A cells. Cytokine transduction in TS/A cells

was often performed isolating clones with different levels of cytokine production, and this allowed to study the dose-related effects, such as the minimal cytokine release level required to significantly impact on tumor growth and immunogenicity and the potential side effects of highly-releasing cells. As an example, IFN-γ transduction led to isolate clones with cytokine production ranging from a few IU/ml up to a very high expressor clone (releasing 6000 IU/ml), likely the highest transduced expression ever obtained. Such a panel of IFN-γ releasing clones showed a dose-related growth inhibition and immunogenicity, but also showed potentially important side effects, such as increased lung colonizing ability and other systemic effects [12,136].

The wide portfolio of TS/A cells transduced with different cytokine genes allowed to understand the role played by each cytokine in the modulation of tumor infiltrate composition and its impact on tumor growth [137]. A major role for granulocytes in cytokine-induced tumor debulking was unexpectedly found, along with a continuous cross-talk between leukocytes and lymphocytes. The transduced cytokine drove the composition of the reactive cells elicited, the efficacy of the anti-tumor reaction and the immune memory against the non-transduced tumor. The increased memory reaction is the basis for the use of gene-engineered cells as anticancer vaccines. On the whole, data obtained with engineered TS/A vaccines (Table 2) showed that the most effective cytokines were IFN-γ and IL-12.

TS/A transduction with GM-CSF was performed only once [74], with almost no effect on tumor growth or immunogenicity. On the contrary, GM-CSF engineering of another murine model (B16 melanoma) gave good results [138] and prompted clinical studies. B16 melanoma did not produce spontaneously GM-CSF whereas TS/A abundantly secreted CSFs [16]. The spontaneous CSF production in TS/A did not hamper tumor growth but likely contributed to the tumor-promoting environment, showing that similar cytokines could play opposite roles in tumors of different origin.

Transduction of genes coding for activating pro-drug enzymes (suicide genes) was performed with the main aim to obtain more immunogenic cancer cell vaccines. It was reported that replicating cells were more immunogenic than dead cells [74], so prodrug activation by suicide gene products could switch off partially replicating cell vaccines after the start of the immune response. However, prodrug-induced cancer cell death itself was found to increase the specific immune response [125]. Suicide genes were also included in oncolytic viruses, to enhance their safety profile [128].

Gene therapy approaches to obtain increased TS/A cancer cell immunogenicity gave interesting but, at the same time, unsatisfactory results. Most approaches actually showed increased immunogenicity, but when challenged in therapeutic set up, a minority of mice could be cured, and only when therapy started at the very early phases of metastatic growth [106,112]. Similar conclusions could be drawn for the variety of gene therapy trials conducted in the last three decades with the purpose of increasing tumor immunogenicity through cytokine or costimulatory gene transduction. Therefore, results obtained with TS/A as well as with other experimental gene therapy models predicted the low efficacy found in trials. Combined gene therapy approaches showed better therapeutic activity and prompted new combination immune-gene therapy approaches [99,111].

Gene transduction was applied to the TS/A model to study cancer biology and cancer gene therapy (Table 3). Transduction of the wild-type p53 gene (p53wt), aiming to restore a correct p53 signaling, was performed in vitro and in vivo with a Canarypox vector carrying p53wt, leading to downstream p21 expression with a proapoptotic effect that caused tumor growth inhibition [21]. Tumor rejection was associated with the generation of a specific antitumor immune response in a sarcoma model but not in TS/A, thus confirming the low immunogenicity of the TS/A model system.

TS/A cells were transduced with luciferase gene and green fluorescent protein (GFP) variants and used in studies on imaging techniques (Table 3). TS/A cells were used as recipient for genes coding exogenous antigens as a surrogate to study features of the corresponding immune response (Table 3).

Silencing approaches were performed with retro- and lenti-viral vectors and recently with CRISPR-Cas9 technology. Through silencing, TGF-β1 released by TS/A cells was found to play a suppressive role on graft-versus-tumor reaction [18].

Table 3. TS/A in transduction studies of cancer biology.

Gene categories	Transgenes	Vector/transfer methods	Refs
Oncosuppressors	m-p53wt	Canarypox	[21]
	m-p53wt/mut	VSV (oncolytic)	[139]
Reporter genes	Luciferase	Naked DNA	[140,141]
	β-galactosidase	Naked DNA + polyfection	[142]
	GFP	Adenoviral	[143]
	GFP	Lentiviral	[46]
	EGFP	Lentiviral	[54]
	EGFP	Naked DNA + electroporation	[50]
	EGFP (driven by p21 or CMV promoter)	Naked DNA + electroporation	[144,145]
Silencing	antisense m-TGF-β1	Retroviral	[18]
	Rab27a	Lentiviral	[146]
	Mlh1	CRISPR-Cas9	[147]
	FoxP3	Lentiviral siRNA	[44]
	fragile X mental retardation protein (FMRP)	Lentiviral shRNA	[46]
Surrogate antigens	β-galactosidase	Retroviral	[81,148–150]
	Hemagglutinin	Naked DNA + lipofection	[151,152]
	Leishmania receptor for activated C kinase (LACK)	Naked DNA	[153–155]
	Mycobacterial cell wall-associated 19-kDa lipoprotein		[156]
	Ovalbumin	Naked DNA	[157,158]
Others	Chromogranin A (Vasostatin-1 fragment)	Naked DNA + electroporation	[159–161]
	Extracellular domain of receptor tyrosine kinase Tie2/TEK (ex-TEK)	Naked DNA + calcium phosphate precipitation	[162]
	Apelin	Naked DNA + polyfection	[163]
	Interferon-regulatory factor-1 (IRF-1)	Adenoviral	[43]
	α1,2fucosyltransferase	Naked DNA + lipofection	[164]
	P27VP22	Naked DNA + polyfection	[165]

In search of new genes potentially involved in metastasis of mammary cancer, along with data from human histopathological samples, some studies used TS/A cells for a mechanistic demonstration through silencing approaches. These studies were sometimes performed in parallel with another popular model of murine mammary cancer (4T1), which is more metastatic than TS/A cells (see Section 6). The overexpression of Fragile X mental retardation protein (FMRP) was concordantly related to lung metastases in both models [46]. On the contrary, some disagreement between TS/A and 4T1 was reported concerning the role of the small GTPase Rab27a [146]. Rab27a was involved in exosome secretion. Its silencing inhibited tumor growth and lung metastases in the 4T1 model, but not in TS/A. It should be noted that the authors described TS/A as a non-metastatic tumor model. Since TS/A is actually able to metastasize to lungs, two explanations are possible for such discrepancy: a) Rab27a is not an on/off determinant of metastatic power, but rather a quantitative modulator; b) 4T1 is a clone while TS/A is a polyclonal and heterogeneous cell line. TS/A extensive subculture can have led to drift phenomena with oligoclonal dominance of less metastatic cells, which are well represented in the cell line of origin.

Genetic inactivation through CRISPR/CAS9 technology of the DNA mismatched repair gene *MutL* homologue 1 (MLH1) in TS/A cells, as well as in other non-mammary murine cancer models, led to increased immunogenicity due to accumulation of neoantigens [147]. MLH1-inactivated cells acquired sensitivity to antibodies against checkpoint inhibitors, which now represent the forefront of cancer immunotherapy.

The expression of murine ErbB2 in TS/A cells was exploited to provide experimental evidence of the oncosuppressor role of FoxP3 in mammary cancers, that downmodulated the expression of the ErbB2 oncogene [44]. TS/A cells was also used as a model to study optimization of parameters of gene electrotransfer [50].

6. Comparison with Other Mammary Cancer Models

Modeling mammary cancer in mouse to study tumor–host interactions took advantage of several model systems [3,4,166]. Reordering models according to their intrinsic complexity, we can mention transplantable murine tumors, gene-driven mammary carcinogenic models, human cell lines grown in vitro or in vivo as xenografts and patient-derived xenografts and organoids.

Concerning transplantable murine mammary cancer, the most popular cell line is 4T1, derived from a spontaneous mammary cancer arisen in a BALB/cfC3H female [167–169]. 4T1 share several features with TS/A and with human mammary cancers, such as low immunogenicity and tumor–host interactions. In fact, several studies were performed using in parallel 4T1 and TS/A (see for example Supplementary Table S1, column N), which were considered as biological replicates and generally gave concordant results. We can focus here on the main differences between the two models. 4T1 is a thioguanine-resistant clone derived from a heterogeneous mammary cancer cell line [167,168]. TS/A is a cell line with heterogeneity spanning from morphology to metastatic ability and to CSF production (and therefore tumor–host interactions), as proven by the in vitro isolation of clones with markedly different features [14,40]. Populations with different abilities to metastasize were also isolated from TS/A through in vivo selection procedures [41]. Heterogeneity is a hallmark of mammary cancer, which comprises morphology, differentiation and metastatic ability, but cloned populations at least partially lose such heterogeneity. 4T1 is a highly aggressive clone, with the ability to give rise to a high number of lung metastases following subcutaneous, intravenous or orthotopic cell injections (see for example [146]). Moreover, 4T1 can metastasize to other organs (such as liver and bone) [170]. TS/A is a cell line provided with metastatic ability but giving rise to moderate number of lung metastases following local growth, subcutaneous and intravenous injections or orthotopic administration [10,54]. The lower metastatic ability of the TS/A model can allow to study a wider range of metastasis modulators.

In the last three decades the research on mammary tumor development and malignancy took advantage of transgenic models. One of the most studied models of gene-driven mammary carcinogenesis was that based on the rat HER2/neu oncogene under the transcriptional control of the Mouse Mammary Tumor Virus (MMTV) promoter [171,172]. Transgenic models recapitulated all the transitions from the normal mammary gland to mammary cancer, both from morphological and molecular points of view, and led to essential advancement in comprehension of the carcinogenic process and development of new therapeutic approaches. The reproducible carcinogenic process observed in transgenic models was exploited to study the prevention of tumor progression, including approaches based on immune strategies [173]. Transgene expression is somewhat artificial, concerning both the xenogeneic origin of the oncogene (rat HER2/neu) and the expression driven by a viral promoter. From an immunological point of view, the fast carcinogenesis and the altered immunoreactivity of mice being tolerant to transgene can be significant differences from the human pathogenetic development of mammary cancer. However, the main problems of transgenic models are time-consuming procedures and costs. Cell lines from spontaneous mammary cancer such as TS/A therefore are still widely employed in studies on biological features and new therapeutic approaches.

Human models for mammary cancer comprise cell lines and xenografts [4,166]. Human breast cancer is a heterogeneous disease that, thanks to biomarkers, can be subdivided in different subtypes with prognostic significance [174,175] and subjected to appropriate treatments. The main advantage of human models is that they can reproduce the heterogeneity among tumors, giving researchers the possibility to choose the correct subtype depending on the aim of the research, while the main constraint of human cell lines and xenografts is the lack of immune tumor–host interactions. To identify which subtypes can be modeled by the different murine mammary cancers, a comparison

among gene expression profiles of a panel of murine mammary cancer cell lines including a TS/A variant (clone E1) and profiles of the different human subtypes was performed [13]. E1 showed a non-basal profile, with prevalent features of luminal A and HER2 subtypes (about 50% and 20%–30% probability, respectively). Therefore, a single murine model can mimic a peculiar human subtype, but obviously is limited to the fixed genetic setting of the cell line and does not reflect diverse spectrum of personalized genetic and/or epigenetic alterations of human breast cancers.

To better depict individual mammary cancers, patient-derived xenografts (PDX) [176] and patient-derived organoids (PDO) were proposed [177–179]. Such approaches are more compatible with the need of precision oncology and without concern of species difference. PDX do not allow to study immune interactions (since they are grown in immunodeficient mice), and also present other disadvantages such as the low frequency of tumor take, with a bias toward more aggressive subtypes [180], the cost and the time-consuming procedure. PDO are 3D cultures obtained by dissociated tumor tissue which can be co-cultured with human lymphocytes, thus allowing to investigate tumor microenvironment, anticancer immunotherapy, and other aspects including development of novel therapeutics [181,182].

In conclusion, preclinical models of murine mammary cancer cell lines are still widely used thanks to their possibility to focus on tumor–host interactions comprising the role of stroma, the metastatic process and immune responses. The recent burst of immune-based anti-cancer therapies (see for example checkpoint inhibitors [133,147] and CAR-T [183]) likely will take advantage of murine models comprising mammary cancer cell lines. Other advantages are the low cost and time to obtain results. The possibility to study in parallel several cancer cell lines mimicking different breast cancer subtypes could remain a first-line means to study innovative molecular and therapeutic approaches, which will be then tested in individually precise, more complex human models.

7. Conclusions

The analysis of the main studies exploiting TS/A as a pre-clinical model of mammary cancer allows to draft a profile spanning from molecular alterations to malignant phenotype and immune interactions. This profile should be considered when designing experiments based on TS/A model. Knowledge of this profile can allow inference about the complexity of human breast cancer.

Supplementary Materials: The following are available online at www.mdpi.com/xxx/s1, Table S1: Comprehensive list of papers using TS/A cell variants.

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Conflicts of Interest: The University of Bologna granted to EMD Millipore license for TS/A distribution worldwide. Royalties are destined for oncological research.

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	A	B	C	D	E	F	G	H	I	J	K	L	M	N
1	**Supplementary Table. Comprehensive list of papers using TS/A cell variants.**													
2	Authors	Year	Title	Source title	Volume	Page start	Page end	Type of study	Category	Keyword 1	Keyword 2	Keyword 3	TS/A cell variant	Other murine cell lines
3	Nanni et al.	1983	TS/A: a new metastasizing cell line from a BALB/c spontaneous mammary adenocarcinoma	Clin Exp Metastas	1	373	380	research paper	BIOLMET	heterogeneity	immunogenicity	metastasis	TS/A	
4	Lollini et al.	1984	High-metastatic clones selected in vitro from a recent spontaneous BALB/c mammary adenocarcinoma cell line	Clin Exp Metastas	2	251	259	research paper	BIOLMET	heterogeneity	in vitro selection	metastasis	TS/A clones	
5	Forni et al.	1985	Lymphokine-activated tumor inhibition in vivo. I. The local administration of interleukin 2 triggers nonreactive lymphocytes from tumor-bearing mice to inhibit tumor growth	J Immunol	134	1305	1311	control model	TUMIMM	immune activation	IL2	growth inhibition	TS/A	CE-2
6	Giovarelli et al.	1985	Alloantigen-activated lymphocytes from mice bearing a spontaneous "nonimmunogenic" adenocarcinoma inhibit its growth in vivo by recruiting host immunoreactivity	J Immunol	135	3596	3603	research paper	TUMIMM	immune activation	alloantigens	growth inhibition	TS/A	CE-2
7	Lollini et al.	1985	In vivo reexpression of H-2 antigens in B16 melanoma cells	Exp Clin Immunogenet	2	14	23	control model	TUMIMM	H-2	interferon	in vivo growth	TS/A	B16 variants
8	Nicoletti et al.	1985	Colony-stimulating activity from the new metastatic TS/A cell line and its high- and low-metastatic clonal derivatives	Br J Cancer	52	215	222	research paper	BIOLMET	microenvironment	CSF	metastasis	TS/A, TS/A clones	
9	Werling et al.	1985	Adhesion and spreading characterization of a rat tumor cell system exhibiting different metastatic behavior	Invas Metast	5	270	294	control model	BIOLMET	rat tumor cell system	adhesion	metastasis	TS/A	
10	Cofano et al.	1986	Binding of murine 125I-labelled natural interferon-gamma to murine cell receptors	J Gen Virol	67	1205	1209	research paper	BIOLMET	IFNgamma		growth inhibition	TS/A	L1210, L-929
11	De Giovanni et al.	1986	Dexamethasone modulation of in vitro growth pattern and of lung colonization ability in clones of a metastatic BALB/c mammary carcinoma cell line	Clin Exp Metastas	4	13	23	research paper	BIOLMET	heterogeneity	dexamethasone	metastasis	TS/A, TS/A clones	
12	Forni et al.	1986	Effect of prolonged administration of low doses of dietary retinoids on cell-mediated immunity and the growth of transplantable tumors in mice	J Natl Cancer I	76	527	533	research paper	TUMIMM	immune activation	retinoids	growth inhibition	TS/A	
13	Nanni et al.	1986	Clones with different metastatic capacity and variant selection during metastasis: a problematic relationship	J Natl Cancer I	76	527	533	research paper	BIOLMET	heterogeneity	in vivo selection	metastasis	TS/A in vivo selected variants	
14	Nanni et al.	1986	RMZ: A new cell line from a human alveolar rhabdomyosarcoma. in vitro expression of embryonic myosin	Br J Cancer	54	1009	1014	citation						
15	Clark et al.	1987	Morphological and metastatic murine melanoma variants: Motility, adhesiveness, cell surface and in vivo properties	Br J Cancer	56	577	584	citation						
16	De Giovanni et al.	1987	Heterogeneity and clonal interactions in the TS/A murine mammary adenocarcinoma	Adv Exp Med Biol	233	5	14	research paper	BIOLMET	heterogeneity	clonal interactions	metastasis	TS/A clones	
17	Giovarelli et al.	1987	In vitro and in vivo immunomodulatory activity of an N-9 arginyl hypoxanthine derivative (PCF-39)	Int J Immunopharmaco	9	659	667	research paper	TUMIMM	immune activation	PCF39	growth inhibition	TS/A	
18	Lollini et al.	1987	Interferon-mediated modulation of metastasis and MHC antigens	Adv Exp Med Biol	233	129	139	citation						
19	Lollini et al.	1987	Interferon-mediated enhancement of metastasis. Are MHC antigens involved?	Clin Exp Metastas	5	277	287	citation						
20	Nicoletti et al.	1987	Are colony-stimulating factor-producing cells facilitated in the metastatic process?	Anticancer Res	7	695	700	research paper	BIOLMET	heterogeneity	CSF	metastasis	TS/A in vivo selected variants	
21	Fassio et al.	1988	Functional characterization of murine cell lines expressing high, intermediate, or negative levels of surface receptors for interferon- gamma	J Interferon Res	8	333	341	research paper	BIOLMET	IFNgamma	antiviral activity	growth inhibition	TS/A	EL-4, L1210, K-BALB
22	Garbisa et al.	1988	Different metastatic aggressiveness by murine TS/A clones: ultrastructure, extracellular glycoproteins and type IV collagenolytic activity	Invas Metast	8	177	192	research paper	BIOLMET	heterogeneity	type IV collagenase	metastasis	TS/A clones	BALB/3T3
23	Murphy et al.	1988	Mechanisms of organ selective tumour growth by bloodborne cancer cells	Br J Cancer	57	19	31	citation						
24	Lollini et al.	1989	Modulation by IFN-gamma of the metastatic ability of murine, human, and H-2-transfected tumor cells	Tumori	75	383	388	research paper	BIOLMET	H-2	IFNgamma	metastasis	TS/A clones	B16, B78H1
25	Nanni et al.	1989	Human rhabdomyosarcoma cells in nude mice as a model for metastasis and differentiation	Invas Metast	9	231	241	citation						
26	Nicoletti et al.	1989	In vivo and in vitro production of haemopoietic colony-stimulating activity by murine cell lines of different origin: a frequent finding	Eur J Cancer Clin Oncol	25	1281	1286	research paper	BIOLMET	microenvironment	CSF	leukocytosis	TS/A-E1	B16 and others

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2	Authors	Year	Title	Source title	Volume	Page start	Page end	Type of study	Category	Keyword 1	Keyword 2	Keyword 3	TS/A cell variant	Other murine cell lines
27	Bosco et al.	1990	Low doses of IL-4 injected perilymphatically in tumor-bearing mice inhibit the growth of poorly and apparently nonimmunogenic tumors and induce a tumor-specific immune memory	J Immunol	145	3136	343	research paper	TUMIMM	immune activation	IL4	immune memory	TS/A	CE-2
28	Hock et al.	1991	Interleukin 7 induces CD4+ T cell-dependent tumor rejection	J Exp Med	174	1291	1298	research paper	TUMIMM/GT	engineered cancer cells	IL7	growth inhibition	TS/A	J558L
29	Cavallo et al.	1992	Role of neutrophils and CD4+ T lymphocytes in the primary and memory response to nonimmunogenic murine mammary adenocarcinoma made immunogenic by IL-2 gene	J Immunol	149	3627	3635	research paper	TUMIMM/GT	engineered cancer cells	IL2	growth inhibition	TS/A	
30	Lollini et al.	1992	Ly-6A/E gene is widely expressed among transformed nonhematopoietic cells. Autocrine modulation by interferon	Anticancer Res	12	2245	2252	research paper	TUMIMM	autocrine production	IFNalpha/beta	Ly-6A/E	TS/A	B16 and others
31	Cavallo et al.	1993	Protective and curative potential of vaccination with interleukin-2-gene-transfected cells from a spontaneous mouse mammary adenocarcinoma	Cancer Res	53	5067	5070	research paper	TUMIMM/GT	engineered cancer vaccines	IL2	growth inhibition	TS/A-pc	CE-2
32	Krüger-Krasagakes et al.	1993	Eosinophils infiltrating interleukin-5 gene-transfected tumors do not suppress tumor growth	Eur J Immunol	23	992	995	research paper	TUMIMM/GT	engineered cancer cells	IL5	infiltrating leukocytes	TS/A	J558L
33	Lollini et al.	1993	Inhibition of tumor growth and enhancement of metastasis after transfection of the γ-interferon gene	Int J Cancer	55	320	329	research paper	TUMIMM/GT	engineered cancer cells	IFNgamma	metastasis	TS/A	
34	Modesti et al.	1993	Ultrastructural evidence of the mechanisms responsible for interleukin-4-activated rejection of a spontaneous murine adenocarcinoma	Int J Cancer	53	988	993	research paper	TUMIMM/GT	engineered cancer cells	IL4	growth inhibition	TS/A	
35	Allione et al.	1994	Immunizing and curative potential of replicating and nonreplicating murine mammary adenocarcinoma cells engineered with interleukin (IL)-2, IL-4, IL-6, IL-7, IL-10, tumor necrosis factor alpha, granulocyte- macrophage colony-stimulating factor, and gamma-interferon gene or admixed with conventional adjuvants	Cancer Res	54	6022	6026	research paper	TUMIMM/GT	engineered cancer vaccines	cytokines	immune therapy	TS/A-pc	
36	Ferrantini et al.	1994	IFN-alpha 1 gene expression into a metastatic murine adenocarcinoma (TS/A) results in CD8+ T cell-mediated tumor rejection and development of antitumor immunity. Comparative studies with IFN-gamma-producing TS/A cells	J Immunol	153	4604	4615	research paper	TUMIMM/GT	engineered cancer vaccines	IFNalpha	immune therapy	TS/A-pc	
37	Musiani et al.	1994	Nature and potential of the reactive response to mouse mammary adenocarcinoma cells engineered with interleukin-2, interleukin-4 or interferon-gamma genes	Nat Immun	13	93	101	research paper	TUMIMM/GT	engineered cancer vaccines	cytokines	immune therapy	TS/A-pc	
38	Pericle et al.	1994	An efficient Th2-type memory follows CD8+ lymphocyte-driven and eosinophil-mediated rejection of a spontaneous mouse mammary adenocarcinoma engineered to release IL-4	J Immunol	153	5659	5673	research paper	TUMIMM/GT	engineered cancer vaccines	IL4	immune therapy	TS/A-pc	
39	Cavallo et al.	1995	Co-expression of B7-1 and ICAM-1 on tumors is required for rejection and the establishment of a memory response	Eur J Immunol	25	1154	1162	research paper	TUMIMM/GT	multi-engineered cancer vaccines	costimulatory molecules	immune therapy	TS/A-pc	J558L, EL-4, RMA, B16-F1
40	Cayeux et al.	1995	Tumor cells cotransfected with interleukin-7 and B7.1 genes induce CD25 and CD28 on tumor-infiltrating T lymphocytes and are strong vaccines	Eur J Immunol	25	2325	2331	research paper	TUMIMM/GT	multi-engineered cancer vaccines	IL7, B7	immune therapy	TS/A	J558L
41	Consalvo et al.	1995	5-Fluorocytosine-induced eradication of murine adenocarcinomas engineered to express the cytosine deaminase suicide gene requires host immune competence and leaves an efficient memory.	J Immunol	154	5302	5312	research paper	TUMIMM/GT	engineered cancer vaccines	cytosine deaminase	immune therapy	TS/A-pc	
42	Giovarelli et al.	1995	Local release of IL-10 by transfected mouse mammary adenocarcinoma cells does not suppress but enhances antitumor reaction and elicits a strong cytotoxic lymphocyte and antibody-dependent immune memory	J Immunol	155	3112	3123	research paper	TUMIMM/GT	engineered cancer vaccines	IL10	immune therapy	TS/A-pc	
43	Lollini et al.	1995	Systemic effects of cytokines released by gene-transduced tumor cells: marked hyperplasia induced in small bowel by gamma-interferon transfectants through host lymphocytes	Int J Cancer	61	425	430	research paper	TUMIMM/GT	engineered cancer cells	IFNgamma	systemic effects	TS/A-pc	
44	Lollini and Nanni	1995	Minimal requirements for characterization of cytokine gene-transduced tumor cells: a proposal	J Natl Cancer I	87	1717	1718	review						
45	Lollini et al.	1995	Transduction of genes coding for a histocompatibility (MHC) antigen and for its physiological inducer interferon-gamma in the same cell: efficient MHC expression and inhibition of tumor and metastasis growth	Hum Gene Ther	6	743	752	research paper	TUMIMM/GT	multi-engineered cancer cells	MHC, IFNgamma	growth inhibition	TS/A-pc	
46	Cassoni et al.	1996	Oxytocin and oxytocin-analogue F314 inhibit cell proliferation and tumor growth of rat and mouse mammary carcinomas	Int J Cancer	66	817	820	research paper	PHARM	oxytocin		growth inhibition	TS/A	C26

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2	Authors	Year	Title	Source title	Volume	Page start	Page end	Type of study	Category	Keyword 1	Keyword 2	Keyword 3	TS/A cell variant	Other murine cell lines
47	Lollini et al.	1996	Re:Randomized trial of adjuvant human interferon gamma versus observation in high-risk cutaneous melanoma: a Southwest Oncology Group study.	J Natl Cancer I	88	926	927	review						
48	Martin-Fontecha et al.	1996	Heterogeneous effects of B7-1 and B7-2 in the induction of both protective and therapeutic anti-tumor immunity against different mouse tumors.	Eur J Immunol	26	1851	1859	research paper	TUMIMM/GT	multi-engineered cancer vaccines	costimulatory molecules	immune therapy	TS/A-pc	
49	Musiani et al.	1996	Role of Neutrophils and Lymphocytes in Inhibition of a Mouse Mammary Adenocarcinoma Engineered to Release IL-2, IL-4, IL-7, IL-10, IFN-α, IFN-γ, and TNF-α	Lab Invest	74	146	157	research paper	TUMIMM/GT	engineered cancer vaccines	cytokines	immune therapy	TS/A-pc	
50	Nanni et al.	1996	Therapy of murine mammary carcinoma metastasis with interferon gamma and MHC gene-transduced tumour cells	Br J Cancer	74	1564	1569	research paper	TUMIMM/GT	multi-engineered cancer vaccines	IFNgamma, MHC	metastasis	TS/A-pc	
51	Pericle et al.	1996	Direct killing of interleukin-2-transfected tumor cells by human neutrophils	Int J Cancer	66	367	373	research paper	TUMIMM/GT	engineered cancer cells	IL2	immune therapy	TS/A-pc	
52	Pericle et al.	1996	CD44 Is a Cytotoxic Triggering Molecule on Human Polymorphonuclear Cells	J Immunol	157	4657	4663	research paper	TUMIMM	CD44	hyaluronic acid	cytotoxicity	TS/A	MC1
53	Vagliani et al.	1996	Interleukin 12 potentiates the curative effect of a vaccine based on interleukin 2-transduced tumor cells	Cancer Res	56	467	470	research paper	TUMIMM/GT	engineered cancer vaccines	IL2	systemic rIL12	TS/A	C-26, C-51
54	Zitvogel et al.	1996	Therapy of murine tumors with tumor peptide-pulsed dendritic cells: Dependence on T cells, B7 costimulation, and T helper cell 1-associated cytokines	J Exp Med	183	87	97	research paper	TUMIMM	peptide-pulsed dendritic vaccine	tumor antigens	growth inhibition	TS/A	MCA205
55	Zitvogel et al.	1996	Interleukin-12 and B7.1 co-stimulation cooperate in the induction of effective antitumor immunity and therapy of established tumors	Eur J Immunol	26	1335	1341	research paper	TUMIMM/GT	multi-engineered cancer vaccines	IL12, B7	growth inhibition	TS/A	MCA207
56	Cavallo et al.	1997	Antitumor efficacy of adenocarcinoma cells engineered to produce interleukin 12 (IL-12) or other cytokines compared with exogenous IL-12	J Natl Cancer I	89	1049	1058	research paper	TUMIMM/GT	engineered cancer vaccines	Cytokines	systemic rIL12	TS/A-pc	
57	Cayeux et al.	1997	Influence of gene-modified (IL-7, IL-4, and B7) tumor cell vaccines on tumor antigen presentation	J Immunol	158	2834	2841	research paper	TUMIMM/GT	multi-engineered cancer vaccines	B7, IL7, IL4	antigen presentation	TS/A	MCA205
58	Di Carlo et al.	1997	Interleukin 6 gene-transfected mouse mammary adenocarcinoma: Tumour cell growth and metastatic potential	J Pathol	182	76	85	research paper	BIOLMET/GT	engineered cancer cells	IL6	metastasis	TS/A-pc	
59	Mackey et al.	1997	Protective immunity induced by tumor vaccines requires interaction between CD40 and its ligand, CD154	Cancer Res	57	2569	2574	research paper	TUMIMM	cancer cell vaccine	costimulatory molecules	immune therapy	TS/A	B16-F10, MCA-105
60	Mayordomo et al.	1997	Bone marrow-derived dendritic cells serve as potent adjuvants for peptide-based antitumor vaccines	Stem Cells	15	94	103	review						
61	Musiani et al.	1997	Cytokines, tumour-cell death and immunogenicity: a question of choice	Immunol Today	18	32	36	review						
62	Pericle et al.	1997	Immunocompromised tumor-bearing mice show a selective loss of STAT5a/b expression in T and B lymphocytes	J Immunol	159	2580	2585	research paper	TUMIMM	Immune suppression	STAT5	tumor-bearing mice	TS/A	
63	Salazar-Onfray et al.	1997	Down-regulation of the expression and function of the transporter associated with antigen processing in murine tumor cell lines expressing IL-10	J Immunol	159	3195	3202	citation						
64	Santodonato et al.	1997	Local and systemic antitumor response after combined therapy of mouse metastatic tumors with tumor cells expressing IFN-α and HSVtk: Perspectives for the generation of cancer vaccines	Gene Ther	4	1246	1255	research paper	TUMIMM/GT	multi-engineered cancer vaccines	suicide gene	growth inhibition	TS/A-pc	
65	Scarpa et al.	1997	Extracellular matrix remodelling in a murine mammary adenocarcinoma transfected with the interferon-alpha 1 gene	J Pathol	181	116	123	research paper	BIOLMET/GT	engineered cancer cells	IFNalpha	microenvironment	TS/A-pc	MMF1
66	Stoppacciaro et al.	1997	Genetic modification of a carcinoma with the IL-4 gene increases the influx of dendritic cells relative to other cytokines	Eur J Immunol	27	2375	2382	control model	TUMIMM/GT	engineered cancer cells	IL4	antitumor immunity	TS/A	C26
67	Tuting et al.	1997	Interferon-alpha gene therapy for cancer: retroviral transduction of fibroblasts and particle-mediated transfection of tumor cells are both effective strategies for gene delivery in murine tumor models	Gene Ther	4	1053	1060	research paper	TUMIMM/GT	engineered cancer cells	IFNalpha	growth inhibition	TS/A	MC38, B16
68	Belardelli et al.	1998	The induction of in vivo proliferation of long-lived CD44(hi) CD8+ T cells after the injection of tumor cells expressing IFN-α<inf>1</inf> into syngeneic mice	Cancer Res	58	5795	5802	research paper	TUMIMM/GT	engineered cancer vaccines	IFNalpha	immune therapy	TS/A-pc	C26
69	Chiaramonte et al.	1998	Is mts1 (S100A4) gene involved in the metastatic process modulated by gamma-interferon?	Pathobiology	66	38	40	research paper	BIOLMET	mts1	IFNgamma	metastasis	TS/A	B16, B78H1
70	Coleman et al.	1998	Nonviral interferon α gene therapy inhibits growth of established tumors by eliciting a systemic immune response	Hum Gene Ther	9	2223	2230	research paper	TUMIMM/GT	in vivo gene therapy	IFNalpha	immune therapy	TS/A	RENCA

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2	Authors	Year	Title	Source title	Volume	Page start	Page end	Type of study	Category	Keyword 1	Keyword 2	Keyword 3	TS/A cell variant	Other murine cell lines
71	Couderc et al.	1998	Enhancement of antitumor immunity by expression of CD70 (CD27 ligand) or CD154 (CD40 ligand) costimulatory molecules in tumor cells	Cancer Gene Ther	5	163	175	research paper	TUMIMM/GT	engineered cancer vaccines	costimulatory molecules	immune therapy	TS/A	MCA207
72	Di Carlo et al.	1998	Local release of interleukin-10 by transfected mouse adenocarcinoma cells exhibits pro- and anti-inflammatory activity and results in a delayed tumor rejection	Eur Cytokine Netw	9	61	68	research paper	TUMIMM/GT	engineered cancer vaccines	IL10	growth inhibition	TS/A-pc	
73	Di Carlo et al.	1998	Interaction between endothelial cells and the secreted cytokine drives the fate of an IL4- or an IL5-transduced tumour	J Pathol	186	390	397	research paper	TUMIMM/GT	engineered cancer vaccines	IL4, IL5	microenvironment	TS/A-pc	
74	Favrot and Puisieux	1998	Application of gene transfer in cancer immunotherapy. From experimental data to clinical protocols	Adv Exp Med Biol	451	539	541	review						
75	Nanni et al.	1998	The immune response elicited by mammary adenocarcinoma cells transduced with interferon-gamma and cytosine deaminase genes cures lung metastases by parental cells.	Hum Gene Ther	9	217	224	research paper	TUMIMM/GT	multi-engineered cancer vaccines	IFNgamma, cytosine deaminase	metastasis	TS/A-pc	
76	Petersson et al.	1998	Constitutive IL-10 production accounts for the high NK sensitivity, low MHC class I expression, and poor transporter associated with antigen processing (TAP)-1/2 function in the prototype NK target YAC-1	J Immunol	161	2099	2105	control model	TUMIMM/GT	engineered cancer cells	IL10	antitumor immunity	TS/A	B16, RMA and
77	Puisieux et al.	1998	Canarypox virus-mediated interleukin 12 gene transfer into murine mammary adenocarcinoma induces tumor suppression and long-term antitumoral immunity	Hum Gene Ther	9	2481	2492	research paper	TUMIMM/GT	engineered cancer vaccines	IL12	canarypoxvirus vector	TS/A	
78	Qin et al.	1998	B cells inhibit induction of T cell-dependent tumor immunity	Nat Med	4	627	630	research paper	TUMIMM	Immune suppression	B cell-deficient mice	antitumor immunity	TS/A	
79	Rossi et al.	1998	Inhibition of lung colonisation of a mouse mammary carcinoma by therapeutic vaccination with interferon-α gene-transduced tumor cells	Clin Exp Metastas	16	123	128	research paper	TUMIMM/GT	engineered cancer vaccines	IFNalpha	metastasis	TS/A-pc	
80	Sapino et al.	1998	Oxytocin receptor within the breast: biological function and distribution	Anticancer Res	18	2181	2186	research paper	PHARM	oxytocin		growth inhibition	TS/A	
81	Uckert et al.	1998	Double suicide gene (cytosine deaminase and herpes simplex virus thymidine kinase) but not single gene transfer allows reliable elimination of tumor cells in vivo	Hum Gene Ther	9	855	865	research paper	TUMIMM/GT	multi-engineered cancer vaccines	suicide gene	growth inhibition	TS/A-pc	
82	Zilocchi et al.	1998	Interferon gamma-independent rejection of interleukin 12-transduced carcinoma cells requires CD4+ T cells and Granulocyte/Macrophage colony-stimulating factor	J Exp Med	188	855	865	citation						
83	Zitvogel et al.	1998	Eradication of established murine tumors using a novel cell-free vaccine: dendritic cell-derived exosomes	Nat Med	4	594	600	control model	TUMIMM	exosomes	dendritic cells	antitumor immunity	TS/A	P815
84	Bergamo et al.	1999	In vitro cell cycle arrest, in vivo action on solid metastasizing tumors, and host toxicity of the antimetastatic drug NAMI-A and cisplatin	J Pharmacol Exp Ther	289	559	564	research paper	PHARM	ruthenium	NAMI-A, cisplatin	metastasis	TS/A	Lewis lung carcinoma, MCA
85	Bronte et al.	1999	Unopposed production of granulocyte-macrophage colony-stimulating factor by tumors inhibits CD8+ T cell responses by dysregulating antigen-presenting cell maturation	J Immunol	162	5728	5737	research paper	TUMIMM	Immune suppression	GM-CSF	tumor-bearing mice	TS/A	CT26
86	Cavallo et al.	1999	Immune events associated with the cure of established tumors and spontaneous metastases by local and systemic interleukin 12	Cancer Res	59	414	421	research paper	TUMIMM	tumor-bearing mice	rIL12	immune therapy	TS/A-pc	F1F
87	Cayeux et al.	1999	Direct and indirect T cell priming by dendritic cell vaccines	Eur J Immunol	29	225	234	research paper	TUMIMM	dendritic cell vaccine	betaGal	immune therapy	TS/A	CT26, MCA205, MCA57
88	Giovarelli et al.	1999	A 'stealth effect': Adenocarcinoma cells engineered to express TRAIL elude tumor-specific and allogeneic T cell reactions	J Immunol	163	4886	4893	research paper	TUMIMM/GT	engineered cancer vaccines	TRAIL	antitumor immunity	TS/A-pc	
89	Moro et al.	1999	Induction of therapeutic T-cell immunity by tumor targeting with soluble recombinant B7-immunoglobulin costimulatory molecules	Cancer Res	59	2650	2656	research paper	TUMIMM	costimulatory molecules	recombinant B7	immune therapy	TS/A	RMA
90	Nanni et al.	1999	Cytokine gene therapy: hopes and pitfalls	Ann Oncol	3	261	266	review						
91	Oshikawa et al.	1999	Synergistic inhibition of tumor growth in a murine mammary adenocarcinoma model by combinational gene therapy using IL-12, pro-IL- 18, and IL-1beta converting enzyme cDNA	P Natl Acad Sci U S A	96	13351	13356	research paper	TUMIMM/GT	multi-engineered cancer vaccines	IL12, IL1beta converting enzyme, pro-IL18	combined gene therapy	TS/A	COS7
92	Pacor et al.	1999	In vitro down regulation of ICAM-1 and E-cadherin and in vivo reduction of lung metastases of TS/A adenocarcinoma by a lysozyme derivative	Int J Mol Med	4	369	375	research paper	BIOLMET	lysozyme	adhesion	metastasis	TS/A	

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2	Authors	Year	Title	Source title	Volume	Page start	Page end	Type of study	Category	Keyword 1	Keyword 2	Keyword 3	TS/A cell variant	Other murine cell lines
93	Pacor et al.	1999	Paracrine effects of IL-4 transfection on TS/A adenocarcinoma cells mediate reduced in vivo growth	Pathol Oncol Res	5	110	116	research paper	BIOLMET/GT	engineered cancer cells	IL4	in vitro growth	TS/A-pc	
94	Prigent et al.	1999	Lymphocyte activation gene-3 induces tumor regression and antitumor immune responses	Eur J Immunol	29	3867	3876	research paper	TUMIMM/GT	engineered cancer vaccines	LAG3	growth inhibition	TS/A	MCA205, RENCA
95	Rozera et al.	1999	Interferon (IFN)-β gene transfer into TS/A adenocarcinoma cells and comparison with IFN-α. Differential effects on tumorigenicity and host response	Am J Pathol	154	1211	1222	research paper	TUMIMM/GT	engineered cancer vaccines	IFNbeta	growth inhibition	TS/A	
96	Sava et al.	1999	Treatment of metastases of solid mouse tumours by NAMI-A: comparison with cisplatin, cyclophosphamide and dacarbazine	Anticancer Res	19	969	972	research paper	PHARM	ruthenium	NAMI-A	metastasis	TS/A	Lewis lung carcinoma
97	Schüler et al.	1999	T helper cell type 1-associated and cytotoxic T lymphocyte-mediated tumor immunity is impaired in interleukin 4-deficient mice	J Exp Med	189	803	810	research paper	TUMIMM	immune activation	IL4	immune therapy	TS/A	CT26
98	Thery et al.	1999	Molecular characterization of dendritic cell-derived exosomes. Selective accumulation of the heat shock protein hsc73.	J Cell Biol	147	599	610	research paper	TUMIMM	exosomes	hsc73	dendritic cells	TS/A	
99	Apolloni et al.	2000	Immortalized myeloid suppressor cells trigger apoptosis in antigen- activated T lymphocytes.	J Immunol	165	6723	6730	research paper	TUMIMM	immune suppression	MDSC	apoptosis	TS/A	CT26, L1210, C26
100	Bergamo et al.	2000	Effects of NAMI-A and some related ruthenium complexes on cell viability after short exposure of tumor cells	Anti-Cancer Drugs	11	665	672	research paper	PHARM	ruthenium	NAMI-A	in vitro growth	TS/A	
101	Bishop et al.	2000	Antitumoral effect of a nonviral interleukin-2 gene therapy is enhanced by combination with 5-fluorouracil	Cancer Gene Ther	7	1165	1171	control model	TUMIMM/GT	combination therapy	IL2	antitumor immunity	TS/A	RENCA
102	Bronte et al.	2000	Identification of a CD11b(+)/Gr-1(+)/CD31(+) myeloid progenitor capable of activating or suppressing CD8(+) T cells.	Blood	96	3838	3846	research paper	TUMIMM	immune suppression	MDSC	CD8+ T cells	TS/A	CT26, MBL-2
103	Chen et al.	2000	Eradication of murine mammary adenocarcinoma through HSVtk expression directed by the glucose-starvation inducible grp78 promoter	Breast Cancer Res Tr	59	81	90	research paper	BIOLMET/GT	engineered cancer cells	suicide gene	immune memory	TS/A	
104	Douin-Echinard et al.	2000	The expression of CD70 and CD80 by gene-modified tumor cells induces an antitumor response depending on the MHC status	Cancer Gene Ther	7	1543	1556	research paper	TUMIMM/GT	multi-engineered cancer vaccines	costimulatory molecules	immune therapy	TS/A	B16.F10
105	Giovarelli et al.	2000	Tumor rejection and immune memory elicited by locally released LEC chemokine are associated with an impressive recruitment of APCs, lymphocytes, and granulocytes.	J Immunol	164		3206	research paper	TUMIMM/GT	engineered cancer vaccines	CCL16	immune therapy	TS/A-pc	F1F
106	Kammertoens et al.	2000	Combined chemotherapy of murine mammary tumors by local activation of the prodrugs ifosfamide and 5-fluorocytosine	Cancer Gene Ther	7	629	636	research paper	BIOLMET/GT	engineered xenogeneic cells	suicide gene	growth inhibition	TS/A	GR
107	Magnarin et al.	2000	Increase of tumour infiltrating lymphocytes in mice treated with antimetastatic doses of NAMI-A	Anticancer Res	20	2939	2944	research paper	PHARM	ruthenium	NAMI-A	metastasis	TS/A	Lewis lung carcinoma
108	Martin-Fontecha et al.	2000	Vaccination with mouse mammary adenocarcinoma cells coexpressing B7-1 (CD80) and B7-2 (CD86) discloses the dominant effect of B7-1 in the induction of antitumor immunity	J Immunol	164	698	704	research paper	TUMIMM/GT	multi-engineered cancer vaccines	costimulatory molecules	immune therapy	TS/A	
109	Meazza et al.	2000	Gene transfer of a secretable form of IL-15 in murine adenocarcinoma cells: effects on tumorigenicity, metastatic potential and immune response	Int J Cancer	87	574	581	research paper	TUMIMM/GT	engineered cancer vaccines	IL15	metastasis	TS/A-pc	F1F
110	Mendiratta et al.	2000	Combination of interleukin 12 and interferon alpha gene therapy induces a synergistic antitumor response against colon and renal cell carcinoma	Hum Gene Ther	11	1851	1862	citation						
111	Pacor et al.	2000	In vitro growth of TS/A adenocarcinoma and of the gene transfected TS/A- IL4 line on biological substrates	Anticancer Res	20	191	196	research paper	TUMIMM/GT	engineered cancer cells	IL4	in vitro adhesion	TS/A	
112	Provinciali et al.	2000	Efficacy of cancer gene therapy in aging adenocarcinoma cells engineered to release IL-2 are rejected but do not induce tumor specific immune memory in old mice	Gene Ther	7	624	632	research paper	TUMIMM/GT	engineered cancer vaccines	IL2	aging	TS/A-pc	
113	Rakhmilevich et al.	2000	Interleukin-12 gene therapy of a weakly immunogenic mouse mammary carcinoma results in reduction of spontaneous lung metastases via a T-cell- independent mechanism	Cancer Gene Ther	7	826	838	research paper	TUMIMM/GT	in vivo gene therapy	IL12	metastasis	TS/A	4T1
114	Rovero et al.	2000	DNA vaccination against rat Her-2/Neu p185 more effectively inhibits carcinogenesis than transplantable carcinomas in transgenic BALB/c mice	J Immunol	165	5133	5142	control model	TUMIMM/GT	DNA vaccine	HER2	antitumor immunity	TS/A-pc	TUBO
115	Willimsky and Blankenstein	2000	Interleukin-7/B7.1-encoding adenoviruses induce rejection of transplanted but not nontransplanted tumors	Cancer Res	60	685	692	research paper	TUMIMM/GT	in vivo gene therapy	IL7, B7	adenoviral vector	TS/A	CT26

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116	Zorzet et al.	2000	Lack of in vitro cytotoxicity, associated to increased G<inf>2</inf>-M cell fraction and inhibition of matrigel invasion, may predict in vivo-selective antimetastasis activity of ruthenium complexes	J Pharmacol Exp Ther	295	927	933	research paper	PHARM	ruthenium	NAMI-A	in vitro invasion	TS/A	
117	Bergamo et al.	2001	Tumour cell uptake G2-M accumulation and cytotoxicity of NAMI-A on TS/A adenocarcinoma cells	Anticancer Res	21	1893	1898	research paper	PHARM	ruthenium	NAMI-A	in vitro toxicity	TS/A	
118	Bussolati et al.	2001	111In-labeled 1, 4, 7, 10-tetraazacyclododecane- N, N′, N″, N‴-tetraacetic acid-Lys8-vasotocin: A new powerful radioligand for oxytocin receptor-expressing tumors	Cancer Res	61	4393	4397	research paper	IMAGING	oxytocin		targeted therapy	TS/A	
119	Cavallo et al.	2001	Interleukin 12-activated lymphocytes influence tumor genetic programs	Cancer Res	61	3518	3523	research paper	TUMIMM	immune activation	IL12	gene expression profiling	TS/A	TUBO
120	Cayeux et al.	2001	Decreased generation of anti-tumor immunity after intrasplenic immunization	Eur J Immunol	31	1392	1399	research paper	TUMIMM/GT	engineered cancer vaccines	surrogate antigen	intrasplenic immunization	TS/A	MCA205
121	Dalziel et al.	2001	Mouse ST6Gal sialyltransferase gene expression during mammary gland lactation	Glycobiology	11	407	412	research paper	BIOLMET	ST6Gal	sialyltransferase	mammary cancer	TS/A-MC (alias TS/A-pc)	
122	De Giovanni et al.	2001	Therapy of lung metastases through combined vaccination with carcinoma cells engineered to release IL-13 and IFN-γ	Gene Ther	8	1698	1704	research paper	TUMIMM/GT	engineered cancer vaccines	IFNgamma, IL13	metastasis	TS/A-pc	
123	Di Carlo et al.	2001	The intriguing role of polymorphonuclear neutrophils in antitumor reactions	Blood	97	339	345	review						
124	El mir et al.	2001	A combination of interleukin-2 and 60 nm cationic supramolecular biovectors for the treatment of established tumours by subcutaneous or intranasal administration	Eur J Cancer	37	1053	1060	research paper	TUMIMM/GT	combination therapy	IL2	immune therapy	TS/A	
125	Kummar et al.	2001	Modulation of graft-versus-tumor effects in a murine allogeneic bone marrow transplantation model by tumor-derived transforming growth factor-betal	Biol Blood Marrow Tr	7	25	30	research paper	TUMIMM/GT	Immune suppression	TGFβ1	graft-versus-tumor	TS/A	JC
126	Lambert et al.	2001	Intranodal immunization with tumor lysate-pulsed dendritic cells enhances protective antitumor immunity	Cancer Res	61	641	646	research paper	TUMIMM	dendritic cell vaccine	tumor lysate	intranodal immunization	TS/A	MCA-105
127	Martino et al.	2001	Effective anti-tumor immunity induced in mice by a two-step vaccination protocol	In Vivo	15	425	428	research paper	TUMIMM/GT	engineered cancer vaccines	mycobacterial antigen	immune memory	TS/A	
128	Odin et al.	2001	Canarypox virus expressing wild type p53 for gene therapy in murine tumors mutated in p53	Cancer Gene Ther	8	87	98	research paper	GT	cancer gene therapy	p53	canarypoxvirus vector	TS/A	
129	Pastorino et al.	2001	Generation of high-titer retroviral vector-producing macrophages as vehicles for in vivo gene transfer	Gene Ther	8	431	441	research paper	GT	engineered macrophages	EGFP	in vivo gene transfer	TS/A	Neuro2A, CE-2, NIH3T3
130	Strasly et al.	2001	IL-12 inhibition of endothelial cell functions and angiogenesis depends on lymphocyte-endothelial cell cross-talk	J Immunol	166	3890	3899	research paper	TUMIMM	microenvironment	rIL12	angiogenesis	TS/A	
131	Wolfers et al.	2001	Tumor-derived exosomes are a source of shared tumor rejection antigens for CTL cross-priming	Nat Med	7	297	303	research paper	TUMIMM	exosomes	CTL	antitumor immunity	TS/A	MC38
132	Bergamo et al.	2002	Ruthenium-based NAMI-A type complexes with in vivo selective metastasis reduction and in vitro invasion inhibition unrelated to cell cytotoxicity	Int J Oncol	21	1331	1338	research paper	PHARM	ruthenium	NAMI-A	metastasis	TS/A	B16-F10, Lewis
133	Chtarbova et al.	2002	Murine Nr4a1 and Herpud1 are up-regulated by Wnt-1, but the homologous human genes are independent from β-catenin activation	Biochem J	367	723	728	control model	BIOLMET	cell signaling	Wnt1	tumor-bearing mice	TS/A	C57-MG
134	Colombo and Trinchieri	2002	Interleukin-12 in anti-tumor immunity and immunotherapy	Cytokine Growth F R	13	155	168	review						
135	Colombo et al.	2002	Chromogranin A expression in neoplastic cells affects tumor growth and morphogenesis in mouse models	Cancer Res	62	941	946	research paper	BIOLMET/GT	engineered cancer cells	chromogranin A	growth inhibition	TS/A	RMA
136	Comes et al.	2002	IFN-γ-independent synergistic effects of IL-12 and IL-15 induce anti-tumor immune responses in syngeneic mice	Eur J Immunol	32	1914	1923	research paper	TUMIMM/GT	multi-engineered cancer vaccines	IL12, IL15	antitumor immunity	TS/A-pc	F1F
137	Donnini et al.	2002	Phenotype, antigen-presenting capacity, and migration of antigen-presenting cells in young and old age	Exp Gerontol	37	1097	1112	research paper	TUMIMM	immunogenicity	antigen presentation	aging	TS/A	TUBO
138	Dunussi-Joannopoulos et al.	2002	Efficacious immunomodulatory activity of the chemokine stromal cell-derived factor 1 (SDF-1): local secretion of SDF-1 at the tumor site serves as T-cell chemoattractant and mediates T-cell-dependent antitumor responses	Blood	100	1551	1558	control model	TUMIMM	hSDF1	CXCR4	antitumor immunity	TS/A	C1498, B16F1
139	Fernandez et al.	2002	Genetically engineered vesicular stomatitis virus in gene therapy: application for treatment of malignant disease	J Virol	76	895	904	research paper	BIOLMET/GT	oncolytic virotherapy	IL4/TK	VSV	TS/A	B16-F10
140	Grangeon et al	2002	In vivo induction of antitumor immunity and protection against tumor growth by injection of CD154-expressing tumor cells	Cancer Gene Ther	9	282	288	research paper	TUMIMM/GT	engineered cancer vaccines	costimulatory molecules	antitumor immunity	TS/A	B16-F10

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2	Authors	Year	Title	Source title	Volume	Page start	Page end	Type of study	Category	Keyword 1	Keyword 2	Keyword 3	TS/A cell variant	Other murine cell lines
141	Gri et al.	2002	Antitumor effect of interleukin (IL)-12 in the absence of endogenous IFN-γ: A role for intrinsic tumor immunogenicity and IL-15	Cancer Res	62	4390	4397	research paper	TUMIMM/GT	engineered cancer vaccines	IL12	growth inhibition	TS/A	C26
142	Grizzle et al.	2002	BXD recombinant inbred mice represent a novel T cell-mediated immune response tumor model	Int J Cancer	101	270	279	research paper	TUMIMM	immunogenicity	BXD mice	metastasis	TS/A	
143	Marionneau et al.	2002	Norwalk virus binds to histo-blood group antigens present on gastroduodenal epithelial cells of secretor individuals	Gastroenterology	122	1967	1977	control model	BIOLMET	ABH antigens	fucosyltransferase	Norwalk virus	TS/A	
144	Mazzoni et al.	2002	Myeloid suppressor lines inhibit T cell responses by an NO-dependent mechanism	J Immunol	168	689	695	research paper	TUMIMM	immune suppression	MDSC	nitric oxide	TS/A	
145	Provinciali et al.	2002	Reactive oxygen species modulate Zn2+-induced apoptosis in cancer cells	Free Radic Biol Med	32	431	445	research paper	BIOLMET	reactive oxygen species	zinc	Apoptosis	TS/A	
146	Quaglino et al.	2002	Immunological prevention of spontaneous tumors: A new prospect?	Immunol Lett	80	75	79	review						
147	Sava et al.	2002	Influence of chemical stability on the activity of the antimetastasis ruthenium compound NAMI-A	Eur J Cancer	38	427	435	research paper	PHARM	ruthenium	NAMI-A	metastasis	TS/A	
148	Vicari et al.	2002	Reversal of tumor-induced dendritic cell paralysis by CpG immunostimulatory oligonucleotide and anti-interleukin 10 receptor antibody	J Exp Med	196	541	549	research paper	TUMIMM	antigen presentation	CpG, IL10	antitumor immunity	TS/A	C26, P815, B16, MC38
149	Akbayeva et al.	2003	Synthesis, catalytic properties and biological activity of new water soluble ruthenium cyclopentadienyl PTA complexes [(C5R5)RuCl(PTA)2] (R = H, Me; PTA = 1,3,5-triaza-7-phosphaadamantane)	Chem Commun (Camb)		264	265	research paper	PHARM	ruthenium		in vitro toxicity	TS/A	
150	Bergamo et al.	2003	Distinct effects of dinuclear ruthenium(III) complexes on cell proliferation and on cell cycle regulation in human and murine tumor cell lines	J Pharmacol Exp Ther	305	725	732	research paper	PHARM	ruthenium		in vitro toxicity	TS/A	B16-F10
151	Chini et al.	2003	Improved radiotracing of oxytocin receptor-expressing tumours using the new [111In]-DOTA-Lys8-deamino-vasotocin analogue	Br J Cancer	89	930	936	research paper	IMAGING	oxytocin	DOTA	growth inhibition	TS/A	
152	De Palma et al.	2003	Targeting exogenous genes to tumor angiogenesis by transplantation of genetically modified hematopoietic stem cells	Nat Med	9	789	795	research paper	BIOLMET/GT	engineered hematopoietic stem cells	Tie2/Tek	angiogenesis	TS/A	LLC, B16, N202.1A
153	Douin-Echinard et al.	2003	Involvement of CD70 and CD80 intracytoplasmic domains in the co-stimulatory signal required to provide an antitumor immune response	Int Immunology	15	359	372	research paper	TUMIMM/GT	engineered cancer vaccines	costimulatory molecules	antitumor immunity	TS/A	
154	Jentsch et al.	2003	Seven-fluorochrome mouse M-FISH for high-resolution analysis of interchromosomal rearrangements	Cytogenet Genome Res	103	84	88	research paper	BIOLMET	karyotype	multiplex-FISH	interchromosomal rearrangements	TS/A	TUBO-AG12
155	Jung et al.	2003	CD3/CD28-costimulated T1 and T2 subsets: differential in vivo allosensitization generates distinct GVT and GVHD effects	Blood	102	3439	3446	research paper	TUMIMM	graft-versus-tumor	costimulatory molecules	antitumor immunity	TS/A	
156	Meazza et al.	2003	Tumor rejection by gene transfer of the MHC class II transactivator in murine mammary adenocarcinoma cells	Eur J Immunol	33	1183	1192	research paper	TUMIMM/GT	engineered cancer vaccines	CIITA	antitumor immunity	TS/A-pc	C26, F1F
157	Porosnicu et al.	2003	The Oncolytic Effect of Recombinant Vesicular Stomatitis Virus Is Enhanced by Expression of the Fusion Cytosine Deaminase/Uracil Phosphoribosyltransferase Suicide Gene	Cancer Res	63	8366	8376	research paper	TUMIMM/GT	oncolytic virotherapy	VSV	growth inhibition	TS/A	B16F10
158	Provinciali et al.	2003	Low effectiveness of DNA vaccination against HER-2/neu in ageing	Vaccine	21	843	848	citation						
159	Roca et al.	2003	Hyperthermia inhibits angiogenesis by a plasminogen activator inhibitor 1-dependent mechanism	Cancer Res	63	1500	1507	research paper	BIOLMET	hyperthermia	PAI1	angiogenesis	TS/A	
160	Rosato et al.	2003	The cytotoxic T-lymphocyte response against a poorly immunogenic mammary adenocarcinoma is focused on a single immunodominant class I epitope derived from the gp70 Env product of an endogenous retrovirus	Cancer Res	63	2158	2163	research paper	TUMIMM	antigen presentation	gp70	antitumor immunity	TS/A-pc	CT26, J558
161	Sava et al.	2003	Dual Action of NAMI-A in inhibition of solid tumor metastasis: selective targeting of metastatic cells and binding to collagen	Clin Cancer Res	9	1898	1905	research paper	PHARM	ruthenium	NAMI-A	metastasis	TS/A	
162	Zavaglia et al.	2003	Intercellular trafficking and enhanced in vivo antitumour activity of a non-virally delivered P27-VP22 fusion protein	Gene Ther	100	314	325	research paper	GT	cancer gene therapy	p27/HSV-VP22	non viral delivery	TS/A-pc	3T3, B16 and others
163	Belicchi Ferrari et al.	2004	Synthesis, characterization and biological activity of copper complexes with pyridoxal thiosemicarbazone derivatives. X-ray crystal structure of three dimeric complexes	J Inorg Biochem	98	301	312	research paper	PHARM	in vitro toxicity	copper complexes	growth inhibition	TS/A	

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164	Cao et al.	2004	Global Gene Expression Profiling in Interleukin-12-Induced Activation of CD8+ Cytotoxic T Lymphocytes against Mouse Mammary Carcinoma	Cell Mol Immunol	1	357	366	research paper	TUMIMM	immune activation	IL12	gene expression profiling	TS/A	
165	Cappello et al.	2004	CCL16/LEC powerfully triggers effector and antigen-presenting functions of macrophages and enhances T cell cytotoxicity	J Leukocyte Biol	75	135	142	research paper	TUMIMM	antigen presentation	CCL16	apoptosis	TS/A	F1F
166	Casarsa et al.	2004	TGFbeta1 regulation and collagen-release-independent connective tissue re-modelling by the ruthenium complex NAMI-A in solid tumours	J Inorg Biochem	98	1648	1654	research paper	PHARM	ruthenium	TGFbeta1	metastasis	TS/A	NIH3T3
167	Clément et al.	2004	Expression of sialyl-Tn epitopes on β1 integrin alters epithelial cell phenotype, proliferation and haptotaxis	J Cell Sci	117	5059	5069	research paper	BIOLMET/GT	engineered cancer cells	sialyltransferase	in vitro invasion	TS/A	
168	Cormary et al.	2004	Induction of T-cell antitumor immunity and protection against tumor growth by secretion of soluble human CD70 molecules.	Cancer Gene Ther	11	497	507	research paper	TUMIMM/GT	engineered cancer vaccines	costimulatory molecules	antitumor immunity	TS/A	
169	De Giovanni et al.	2004	APC10.1: An ApcMin/+ intestinal cell line with retention of heterozygosity	Int J Cancer	109	200	206	citation						
170	Di Carlo et al.	2004	IL-21 Induces Tumor Rejection by Specific CTL and IFN-γ-Dependent CXC Chemokines in Syngeneic Mice	J Immunol	172	1540	1547	research paper	TUMIMM/GT	engineered cancer vaccines	IL21	antitumor immunity	TS/A-pc	C26
171	Ferrari et al.	2004	Synthesis, characterization and biological activity of copper complexes with pyridoxal thiosemicarbazone derivatives. X-ray crystal structure of three dimeric complexes	J Inorg Biochem	98	301	312	research paper	PHARM	in vitro toxicity	copper complexes	growth inhibition	TS/A	
172	Guiducci et al.	2004	Intralesional Injection of Adenovirus Encoding CC Chemokine Ligand 16 Inhibits Mammary Tumor Growth and Prevents Metastatic-Induced Death after Surgical Removal of the Treated Primary Tumor	J Immunol	172	4026	4036	research paper	TUMIMM/GT	in vivo gene therapy	CCL16	adenoviral vector	TS/A	4T1
173	Hahn et al.	2004	Viral vector-mediated transduction of a modified thrombospondin-2 cDNA inhibits tumor growth and angiogenesis	Gene Ther	11	739	745	research paper	BIOLMET/GT	cancer gene therapy	Nftsp2	angiogenesis	TS/A	NIH3T3
174	Kim et al.	2004	IRF-1 expression induces apoptosis and inhibits tumor growth in mouse mammary cancer cells in vitro and in vivo	Oncogene	23	1125	1135	research paper	BIOLMET/GT	engineered cancer cells	IRF1	apoptosis	TS/A	C3-L5
175	Kurte et al.	2004	A synthetic peptide homologous to functional domain of human IL-10 down-regulates expression of MHC class I and Transporter associated with Antigen Processing 1/2 in human melanoma cells	J Immunol	173	1731	1737	citation						
176	Malosio et al.	2004	Dense-core granules: a specific hallmark of the neuronal/neurosecretory cell phenotype	J Cell Sci	117	743	749	control model	BIOLMET	engineered cancer cells	chromogranin A	neurosecretory phenotype	TS/A	PC12
177	Margiotta et al.	2004	Antiviral properties and cytotoxic activity of platinum(II) complexes with 1,10-phenanthrolines and acyclovir or penciclovir	J Inorg Biochem	98	1385	1390	research paper	PHARM	platinum complexes	Me_2phen	cytotoxicity	TS/A	
178	Melani et al.	2004	Angiopoietin decoy secreted at tumor site impairs tumor growth and metastases by inducing local inflammation and altering neoangiogenesis	Cancer Immunol Immunother	53	600	608	research paper	TUMIMM/GT	cancer gene therapy	angiopoietin decoy	metastasis	TS/A	C26
179	Mitsuhashi et al.	2004	Regulation of interleukin-12 gene expression and its anti-tumor activities by prostaglandin E2 derived from mammary carcinomas	J Leukocyte Biol	76	322	332	research paper	TUMIMM	immune activation	PGE2	systemic rIL12	TS/A	4T1
180	Morini et al.	2004	Prevention of angiogenesis by naked DNA IL-12 gene transfer: angioprevention by immunogene therapy	Gene Ther	11	284	291	research paper	TUMIMM/GT	in vivo gene therapy	IL12	angiogenesis	TS/A	
181	Reome et al.	2004	Type 1 and type 2 tumor infiltrating effector cell subpopulations in progressive breast cancer	Clin Immunol	111	69	81	research paper	TUMIMM	TIL	NKT	antitumor immunity	TS/A	
182	Sacchi et al.	2004	Crucial role for interferon γ in the synergism between tumor vasculature-targeted tumor necrosis factor α (NGR-TNF) and doxorubicin	Cancer Res	64	7150	7155	research paper	BIOLMET/GT	tumor vascular targeting	IFNgamma	doxorubicin	TS/A	B16
183	Sakai et al.	2004	Vaccination by genetically modified dendritic cells expressing a truncated neu oncogene prevents development of breast cancer in transgenic mice	Cancer Res	64	8022	8028	control model	TUMIMM/GT	HER2+ breast cancer	adenoviral vaccine	antitumor immunity	TS/A	TUBO, N202.1A
184	Serafini et al.	2004	Derangement of immune responses by myeloid suppressor cells	Cancer Immunol Immunother	53	64	72	review						
185	Turel et al.	2004	Solution, solid state and biological characterization of ruthenium(III)-DMSO complexes with purine base derivatives	J Inorg Biochem	98	393	401	research paper	PHARM	ruthenium	adhesion	in vitro growth	TS/A	

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186	Velders et al.	2004	Synthesis and Chemical-Pharmacological Characterization of the Antimetastatic NAMI-A-Type Ru(III) Complexes (Hdmtp)[trans-RuCl4(dmso-S)(dmtp)], (Na)[trans-RuCl4(dmso-S)(dmtp)], and [mer-RuCl3(H2O)(dmso-S)(dmtp)] (dmtp) 5,7 Dimethyl[1,2,4]triazolo[1,5a]pyrimidine)	J Med Chem	47	1110	1121	research paper	PHARM	ruthenium	NAMI-A	metastasis	TS/A	B16-F10
187	Weber et al.	2004	IL-12 cDNA direct injection: antimetastatic effect from a single injection in a murine hepatic metastases model	J Surg Res	122	210	217	research paper	TUMIMM/GT	in vivo gene therapy	IL12	metastasis	TS/A	
188	Benigni et al.	2005	Phenotype and homing of CD4 tumor-specific T cells is modulated by tumor bulk	J Immunol	175	739	748	research paper	TUMIMM/GT	engineered cancer cells	CD4 homing	antitumor immunity	TS/A	
189	Casares et al.	2005	Caspase-dependent immunogenicity of doxorubicin-induced tumor cell death	J Exp Med	202	1691	1701	control model	TUMIMM	immune activation	doxorubicin	caspase	TS/A	CT26,B16F10
190	Di Carlo et al.	2005	Immunological mechanisms elicited at the tumour site by lymphocyte activation gene-3 (LAG-3) versus IL-12: Sharing a common Th1 anti-tumour immune pathway	J Pathol	205	82	91	research paper	TUMIMM/GT	engineered cancer cells	LAG3	antitumor immunity	TS/A	
191	Foley et al.	2005	Ex vivo rapamycin generates donor Th2 cells that potently inhibit graft-versus-host disease and graft-versus-tumor effects via an IL-4-dependent mechanism.	J Immunol	175	5732	5743	research paper	TUMIMM	graft-versus-tumor	rapamycin	growth inhibition	TS/A	
192	Garanger et al.	2005	New multifunctional molecular conjugate vector for targeting, imaging, and therapy of tumors	Mol Ther	12	1168	1175	research paper	GT	in vivo gene therapy	alphaVbeta3	RAFT vector	TS/A-pc	
193	Guiducci et al.	2005	Redirecting in vivo elicited tumor infiltrating macrophages and dendritic cells towards tumor rejection	Cancer Res	65	3437	3446	research paper	TUMIMM/GT	TAM	CCL16	adenoviral vector	TS/A	MCA38, 4T1
194	Hsu et al.	2005	Genetic regulation of thymic involution	Mech Ageing Dev	126	87	97	review						
195	Park et al.	2005	Early role of CD4+Th1 cells and antibodies in HER-2 adenovirus vaccine protection against autochthonous mammary carcinomas	J Immunol	174	4228	4236	control model	TUMIMM/GT	HER2+ breast cancer	in vivo gene therapy	adenoviral vaccine	TS/A	TUBO, N202.1A, N202.1E
196	Preiss et al.	2005	Tumor-induced antibodies resemble the response to tissue damage	Int J Cancer	115	456	462	research paper	TUMIMM	tumor-induced antibodies	tissue damage	growth inhibition	TS/A	
197	Scolaro et al.	2005	In vitro and in vivo evaluation of ruthenium(II)-arene PTA complexes	J Med Chem	48	4161	4171	research paper	PHARM	ruthenium	RAPTA-C	metastasis	TS/A	
198	Agu et al.	2006	The cytotoxic activity of the bacteriophage λ-holin protein reduces tumour growth rates in mammary cancer cell xenograft models	J Gene Med	8	229	241	research paper	GT	cancer gene therapy	λ holin	growth inhibition	TS/A	
199	Come et al.	2006	CD25+regulatory T cell depletion augments immunotherapy of micrometastases by an IL-21-secreting cellular vaccine	J Immunol	176	1750	1758	research paper	TUMIMM/GT	engineered cancer vaccines	IL21	Treg	TS/A	F1F
200	Dobrzanski et al.	2006	CD8-mediated type 1 antitumor responses selectively modulate endogenous differentiated and nondifferentiated T cell localization, activation, and function in progressive breast cancer	J Immunol	177	8191	8201	research paper	TUMIMM/GT	antigen presentation	surrogate antigen	antitumor immunity	TS/A	
201	Grimaldi et al.	2006	Anandamide inhibits adhesion and migration of breast cancer cells	Exp Cell Res	312	363	373	research paper	PHARM	anandamide	CB_1 receptor	in vitro adhesion	TS/A-E1	
202	Liu et al.	2006	Murine mammary carcinoma exosomes promote tumor growth by suppression of NK cell function	J Immunol	176	1375	1385	research paper	TUMIMM	exosomes	NK	antitumor immunity	TS/A	4T1
203	Mortara et al.	2006	CIITA-induced MHC class II expression in mammary adenocarcinoma leads to a Th1 polarization of the tumor microenvironment, tumor rejection, and specific antitumor memory	Clin Cancer Res	12	3435	3443	research paper	TUMIMM/GT	engineered cancer vaccines	CIITA	immune memory	TS/A	C26, F1F
204	Richards et al.	2006	Tumor growth impedes natural-killer-cell maturation in the bone marrow	Blood	108	246	252	research paper	TUMIMM	immune suppression	NK	antitumor immunity	TS/A	4T1, EL-4, RMA-s, MC38, B16-F1
205	Schirmbeck et al.	2006	Priming protective CD8 T cell immunity by DNA vaccines encoding chimeric, stress protein-capturing tumor-associated antigen	J Immunol	177	1534	1542	research paper	TUMIMM/GT	DNA vaccine	gp70	cancer prevention	TS/A	CT26, P815, RBL5/EL4, mKSA
206	Scolaro et al.	2006	Influence of hydrogen-bonding substituents on the cytotoxicity of RAPTA compounds	Organometallics	25	756	765	research paper	PHARM	ruthenium	RAPTA-C	drug uptake	TS/A	

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2	Authors	Year	Title	Source title	Volume	Page start	Page end	Type of study	Category	Keyword 1	Keyword 2	Keyword 3	TS/A cell variant	Other murine cell lines
207	Serafini et al.	2006	Phosphodiesterase-5 inhibition augments endogenous antitumor immunity by reducing myeloid-derived suppressor cell function	J Exp Med	203	2691	2702	research paper	TUMIMM	immune suppression	MDSC	antitumor immunity	TS/A	CT26, MCA203, B16-GM, 4T1-HA
208	Valzasina et al.	2006	Tumor-induced expansion of regulatory T cells by conversion of CD4+CD25- lymphocytes is thymus and proliferation independent	Cancer Res	66	4488	4495	research paper	TUMIMM	immune escape	Treg	antitumor immunity	TS/A	CT26, 4T1
209	Vock et al.	2006	Synthesis, characterization, and in vitro evaluation of novel ruthenium(II) η6-arene imidazole complexes	J Med Chem	49	5552	5561	research paper	PHARM	ruthenium		cytotoxicity	TS/A	
210	Yurkovetsky et al.	2006	Comparative analysis of antitumor activity of CD40L, RANKL, and 4-1BBL in vivo following intratumoral administration of viral vectors or transduced dendritic cells	J Gene Med	8	129	137	research paper	TUMIMM/GT	in vivo gene therapy	cancer vaccines	growth inhibition	TS/A	MC38
211	Braschoss et al.	2007	New anti-CD30 human pancreatic ribonuclease-based immunotoxin reveals strong and specific cytotoxicity in vivo	Leukemia Lymphoma	48	1179	1186	research paper	TUMIMM	immunotoxin		antitumor immunity	TS/A	
212	Croci et al.	2007	Expression of a functional CCR7 chemokine receptor inhibits the post-intravasation steps of metastasis in malignant murine mammary cancer cells	Oncol Rep	18	451	456	research paper	TUMIMM/GT	engineered cancer vaccines	CCR7	metastasis	TS/A	N202.1A
213	Faneca et al.	2007	Evaluation of the antitumoral effect mediated by IL-12 and HSV-tk genes when delivered by a novel lipid-based system	Biochim Biophys Acta - Biomembranes	1768	1093	1102	research paper	GT	in vivo gene therapy	lipid-based system	growth inhibition	TS/A	
214	Fuchs et al.	2007	A cleavable molecular adapter reduces side effects and concomitantly enhances efficacy in tumor treatment by targeted toxins in mice	J Control Release	117	342	350	research paper	PHARM	targeting	saporin	growth inhibition	TS/A	
215	Grizzle et al.	2007	Age-related increase of tumor susceptibility is associated with myeloid-derived suppressor cell mediated suppression of T cell cytotoxicity in recombinant inbred BXD12 mice	Mech Ageing Dev	128	672	680	research paper	TUMIMM	immune suppression	MDSC	aging	TS/A	
216	Josserand et al.	2007	Non-invasive in vivo optical imaging of the lacZ and luc gene expression in mice	Gene Ther	14	1587	1593	research paper	IMAGING	engineered cancer cells	luciferase, betaGal	in vivo imaging	TS/A-pc	
217	Li et al.	2007	Cross-talk between T cells and innate immune cells is crucial for IFN-γ-dependent tumor rejection	J Immunol	179	1568	1576	research paper	TUMIMM	immune activation	IFNgamma	antitumor immunity	TS/A	MCA205, J558L
218	Liu et al.	2007	Expansion of spleen myeloid suppressor cells represses NK cell cytotoxicity in tumor-bearing host	Blood	109	4336	4342	research paper	TUMIMM	immune suppression	MDSC	antitumor immunity	TS/A	YAC-1
219	Mortara et al.	2007	Experimental therapeutic approaches to adenocarcinoma: the potential of tumor cells engineered to express MHC class II molecules combined with naked DNA interleukin-12 gene transfer	Surg Oncol	16, suppl 1	S33	S36	review						
220	Obeid et al.	2007	Ecto-calreticulin in immunogenic chemotherapy	Immunol Rev	220	22	34	review						
221	Sancey et al.	2007	In vivo imaging of tumour angiogenesis in mice with the alpha(v)beta (3) integrin-targeted tracer 99mTc-RAFT-RGD.	Eur J Nucl Med Mol I	34	2037	2047	research paper	IMAGING	in vivo imaging	alphaVbeta3	angiogenesis	TS/A-pc	B16F0
222	Scolaro et al.	2007	Tuning the hydrophobicity of ruthenium(II)-arene (RAPTA) drugs to modify uptake, biomolecular interactions and efficacy	Dalton Transactions		5065	5072	research paper	PHARM	ruthenium	hydrophobicity	cytotoxicity	TS/A	
223	Sorli et al.	2007	Apelin is a potent activator of tumour neoangiogenesis	Oncogene	26	7692	7699	research paper	BIOLMET/GT	engineered cancer cells	apelin	angiogenesis	TS/A	
224	Steel et al.	2007	Immunocompetent syngeneic cotton rat tumor models for the assessment of replication-competent oncolytic adenovirus	Virology	369	131	142	research paper	BIOLMET	oncolytic virotherapy	adenovirus	growth inhibition	TS/A	15-12RM
225	Yamano et al.	2007	Immunity against breast cancer by TERT DNA vaccine primed with chemokine CCL21	Cancer Gene Ther	14	451	459	research paper	TUMIMM/GT	DNA vaccine	TERT	antitumor immunity	TS/A	B16, 4T1
226	Yu et al.	2007	Tumor exosomes inhibit differentiation of bone marrow dendritic cells	J Immunol	178	6867	6875	research paper	TUMIMM	exosomes	dendritic cells	antitumor immunity	TS/A	B16
227	Zhang et al.	2007	Curcumin reverses breast tumor exosomes mediated immune suppression of NK cell tumor cytotoxicity	Biochim Biophys Acta	1773	1116	1123	research paper	TUMIMM	exosomes	NK	antitumor immunity	TS/A	4T1
228	Zimmermann et al.	2007	Tumors hamper the immunogenic competence of CD4+T cell-directed dendritic cell vaccination	J Immunol	179	2899	2909	research paper	TUMIMM	dendritic cell vaccine	CD4+	antitumor immunity	TS/A	
229	Zuo et al.	2007	FOXP3 is an X-linked breast cancer suppressor gene and an important repressor of the HER-2/ErbB2 oncogene	Cell	129	1275	1286	research paper	BIOLMET/GT	engineered cancer cells	HER2, FOXP3	growth inhibition	TS/A	4T1

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230	Dobrzanski et al.	2008	Ag-specific type 1 CD8 effector cells enhance methotrexate-mediated antitumor responses by modulating differentiated T cell localization, activation and chemokine production in established breast cancer	Clin Immunol	37	315	338	research paper	TUMIMM	antigen presentation	methotrexate	antitumor immunity	TS/A	
231	Komita et al.	2008	CD8+ T-cell responses against hemoglobin-beta prevent solid tumor growth	Cancer Res	68	8076	8084	research paper	TUMIMM/GT	engineered dendritic cell vaccine	hemoglobin-beta	growth inhibition	TS/A	CMS4, MethA, CT26
232	Piconese et al.	2008	OX40 triggering blocks suppression by regulatory T cells and facilitates tumor rejection	J Exp Med	205	825	839	research paper	TUMIMM	Treg	OX40	growth inhibition	TS/A	CT26, N2C, MCA203
233	Bachran et al.	2009	Inhibition of tumor growth by targeted toxins in mice is dramatically improved by saponinum album in a synergistic way	J Immunother	32	713	725	research paper	PHARM	targeting	saporin	growth inhibition	TS/A	
234	Bierer, B.E.	2009	Animal models for tumor immunology	Curr Prot Immunol	85	20.0.1	20.0.9	review						
235	Cai et al.	2009	Optimized systemic dosing with CpG DNA enhances dendritic cell-mediated rejection of a poorly immunogenic mammary tumor in BALB/c mice	Clin Transl Sci	2	62	66	research paper	TUMIMM	dendritic cell vaccine	CpG	growth inhibition	TS/A	
236	Dewan et al.	2009	Fractionated but not single-dose radiotherapy induces an immune-mediated abscopal effect when combined with anti-CTLA-4 antibody	Clin Cancer Res	15	5379	5388	research paper	PHARM	radiotherapy	abscopal effect	growth inhibition	TS/A	MCA38
237	Ghiringhelli et al.	2009	Activation of the NLRP3 inflammasome in dendritic cells induces IL-1beta-dependent adaptive immunity against tumors	Nat Med	15	1170	1178	research paper	TUMIMM	immune activation	inflammasome	antitumor immunity	TS/A	EG7, EL4, MCA2, CT26, B16F10
238	Hirsch et al.	2009	Anti-CD30 human IL-2 fusion proteins display strong and specific cytotoxicity In Vivo	Curr Drug Targets	10	110	117	research paper	TUMIMM/GT	fusion protein	CD30	antitumor immunity	TS/A	J558L
239	Lu et al.	2009	Responsiveness of stromal fibroblasts to IFN-γ blocks tumor growth via angiostasis	J Immunol	183	6413	6421	control model	TUMIMM	TAF	IFNalpha	angiogenesis	TS/A	FH32, MCA205, J558L
240	Mirshahidi et al.	2009	Overlapping synthetic peptides encoding TPD52 as breast cancer vaccine in mice: prolonged survival	Vaccine	27	1825	1833	research paper	TUMIMM	peptide-based vaccines	tumor protein D52	antitumor immunity	TS/A	P815
241	Mortara et al.	2009	Irradiated CIITA-positive mammary adenocarcinoma cells act as a potent anti-tumor-preventive vaccine by inducing tumor-specific CD4+T cell priming and CD8+T cell effector functions	Int Immunology	21	655	665	research paper	TUMIMM/GT	engineered cancer vaccines	CIITA	antitumor immunity	TS/A	C26, F1F
242	Sancey et al.	2009	Drug development in oncology assisted by noninvasive optical imaging	Int J Pharm	379	309	316	research paper	PHARM	imaging	lipid-based system	apoptosis	TS/A-pc	
243	Texier et al.	2009	Cyanine-loaded lipid nanoparticles for improved in vivo fluorescence imaging	J Biomed Opt	14	54005-1	54005-11	research paper	IMAGING	targeting	lipid-based system	cyanine dyes	TS/A-pc	
244	Accolla et al.	2010	New strategies of mammary cancer vaccination	Breast J	16	S42	S44	review						
245	Frangione et al.	2010	CIITA-driven MHC-II positive tumor cells: preventive vaccines and superior generators of antitumor CD4+ T lymphocytes for immunotherapy	Int J Cancer	127	1614	1624	research paper	TUMIMM/GT	engineered cancer vaccines	CIITA	antitumor immunity	TS/A	C51, RENCA, WEHI-164
246	Goutayer et al.	2010	Tumor targeting of functionalized lipid nanoparticles: assessment by in vivo fluorescence imaging	Eur J Pharm Biopharm	75	137	147	research paper	PHARM	targeting	lipid-based system	imaging	TS/A-pc	
247	Huang et al.	2010	Deoxyelephantopin, a novel multifunctional agent, suppresses mammary tumour growth and lung metastasis and doubles survival time in mice	Br J Pharmacol	159	856	871	research paper	PHARM	chemoprevention	deoxyelephantopin	metastasis	TS/A	
248	Kim et al.	2010	Ras activation contributes to the maintenance and expansion of Sca-1poscells in a mouse model of breast cancer	Cancer Lett	287	172	181	research paper	BIOLMET	cancer stem cells	Ras	Sca1	TS/A	4T1, EMT6 and CT26
249	Lee et al.	2010	Differential proteomic profiling identifies novel molecular targets of paclitaxel and phytoagent deoxyelephantopin against mammary adenocarcinoma cells	J Proteome Res	9	237	253	research paper	PHARM	drug activity	paclitaxel, deoxyelephantopin	proteomic profiling	TS/A	
250	Lipnik et al.	2010	Interferon γ-Induced human guanylate binding protein 1 inhibits mammary tumor growth in mice	Mol Med	16	177	187	research paper	TUMIMM/GT	engineered cancer cells	hGBP1	angiogenesis	TS/A	
251	Liu et al.	2010	Contribution of MyD88 to the Tumor Exosome-Mediated Induction of Myeloid Derived Suppressor Cells	Blood	176	2490	2499	citation						
252	Movahedi et al.	2010	Different Tumor Microenvironments Contain Functionally Distinct Subsets of Macrophages Derived from Ly6C(high)Monocytes	Cancer Res	70	5728	5739	research paper	TUMIMM	immune suppression	MDSC	microenvironment	TS/A	4T1, 3LL-R
253	Schiering et al.	2010	Antigen-experienced CD4+ T cells limit naïve T-cell priming in response to therapeutic vaccination in vivo	Cancer Res	70	6161	6170	research paper	TUMIMM	cancer cell vaccine	surrogate antigen	antitumor immunity	TS/A	

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254	Cottone et al.	2011	Evaluation of the role of tumor-associated macrophages in an experimental model of peritoneal carcinomatosis using 18F-FDG PET	J Nucl Med	52	1770	1777	research paper	IMAGING	PET	TAM	peritoneal carcinomatosis	TS/A	
255	Daftarian et al.	2011	Peptide-conjugated PAMAM dendrimer as a universal DNA vaccine platform to target antigen-presenting cells	Cancer Res	71	7452	7462	research paper	TUMIMM/GT	DNA-peptide-dendrimer vaccines	gp70	antitumor immunity	TS/A	B16-F10, MBL-2, CT26
256	Heiber and Barber	2011	Vesicular stomatitis virus expressing tumor suppressor p53 is a highly attenuated, potent oncolytic agent	J Virol	85	10440	10450	research paper	BIOLMET/GT	oncolytic virotherapy	p53	VSV	TS/A	mouse embryonic fibroblasts
257	Iezzi et al.	2011	HCG hastens both the development of mammary carcinoma and the metastatization of HCG/LH and ERBB-2 receptor-positive cells in mice	Int J Immunopath Ph	24	621	630	control model	BIOLMET	HER2+ breast cancer	hCG	metastasis	TS/A	TUBO
258	Kamensek et al.	2011	Irradiation, cisplatin, and 5-azacytidine upregulate cytomegalovirus promoter in tumors and muscles: Implementation of non-invasive fluorescence imaging	Mol Imaging Biol	13	43	52	research paper	GT	cancer gene therapy	GFP	CMV promoter	TS/A	LPB
259	Leveille et al.	2011	Vesicular stomatitis virus oncolytic treatment interferes with tumor-associated dendritic cell functions and abrogates tumor antigen presentation	Cancer Gene Ther	85	12160	12169	research paper	TUMIMM/GT	oncolytic virotherapy	antigen presentation	VSV	TS/A	PC3, B16-F10
260	Li et al.	2011	Identification of a tumor suppressor relay between the FOXP3 and the Hippo pathways in breast and prostate cancers	Cancer Res	71	2162	2171	research paper	BIOLMET/GT	tumor suppressor	FOXP3	growth inhibition	TS/A	
261	Schmieder et al.	2011	Synergistic activation by p38MAPK and glucocorticoid signaling mediates induction of M2-like tumor-associated macrophages expressing the novel CD20 homolog MS4A8A.	Int J Cancer	129	122	132	research paper	BIOLMET	TAM	CD20	Gene expression profiling	TS/A	B16F1
262	Sinha et al.	2011	Myeloid-derived suppressor cells express the death receptor Fas and apoptose in response to T cell-expressed FasL	Blood	117	5381	5390	research paper	BIOLMET	immune suppression	MDSC	apoptosis	TS/A	4T1, AT3
263	Veschini	2011	The vasostatin-1 fragment of chromogranin A preserves a quiescent phenotype in hypoxia-driven endothelial cells and regulates tumor neovascularization.	FASEB J	25	3906	3914	research paper	BIOLMET/GT	engineered cancer cells	vasostatin1	angiogenesis	TS/A	
264	Bobrie et al.	2012	Rab27a supports exosome-dependent and -independent mechanisms that modify the tumor microenvironment and can promote tumor progression	Cancer Res	72	4920	4930	research paper	BIOLMET	exosomes	microenvironment	tumor progression	TS/A	4T1
265	Coral et al.	2012	Epigenetic remodelling of gene expression profiles of neoplastic and normal tissues: Immunotherapeutic implications	Br J Cancer	107	1116	1124	research paper	TUMIMM	epigenetic modulation	gene expression profiling	antitumor immunity	TS/A	
266	Dewan et al.	2012	Synergy of topical toll-like receptor 7 agonist with radiation and low-dose cyclophosphamide in a mouse model of cutaneous breast cancer.	Clin Cancer Res	18	6668	6678	research paper	BIOLMET	combination therapy	TLR7	metastasis	TS/A	
267	Lee and Shyur	2012	Deoxyelephantopin impedes mammary adenocarcinoma cell motility by inhibiting calpain-mediated adhesion dynamics and inducing reactive oxygen species and aggresome formation.	Free Radic Biol Med	52	1423	1436	research paper	PHARM	calpain	deoxyelephantopin	motility	TS/A	
268	Morandi et al.	2012	Dendritic cell editing by activated natural killer cells results in a more protective cancer-specific immune response	PLoS ONE	7	e39170		research paper	TUMIMM	immune activation	dendritic cells	antitumor immunity	TS/A	YAC-1
269	Ostrand-Rosenberg et al.	2012	Regulating the suppressors: apoptosis and inflammation govern the survival of tumor-induced myeloid-derived suppressor cells (MDSC)	Cancer Immunol Immunother	61	1319	1325	research paper	TUMIMM	immune suppression	MDSC	proteomic profiling	TS/A	4T1, AT3
270	Sedlar et al.	2012	Potentiation of electrochemotherapy by intramuscular IL-12 gene electrotransfer in murine sarcoma and carcinoma with different immunogenicity	Radiol Oncol	46	302	311	research paper	GT	electrochemotherapy	IL12	growth inhibition	TS/A	SA-1
271	Shibue et al.	2012	The outgrowth of micrometastases is enabled by the formation of filopodium-like protrusions	Cancer Discov	2	706	721	research paper	BIOLMET	motility	filopodium-like protrusions	metastasis	TS/A	D2
272	Sinha et al.	2012	Tumor-induced myeloid-derived suppressor cell function is independent of IFN-γ and IL-4Rα	Eur J Immunol	42	2052	2059	research paper	TUMIMM	immune suppression	MDSC	antitumor immunity	TS/A	CT26, 4T1, B16, MC38, 3LL
273	Arigoni et al.	2013	MiR-135b coordinates progression of ErbB2-driven mammary carcinomas through suppression of MID1 and MTCH2	Am J Pathol	182	2058	2070	control model	BIOLMET	HER2+ breast cancer	miR-135b	tumor progression	TS/A	4T1, TUBO
274	Ben Yebdri et al.	2013	Triptolide-mediated inhibition of interferon signaling enhances vesicular stomatitis virus-based oncolysis.	Mol Ther	21	2043	2053	research paper	BIOLMET	oncolytic virotherapy	triptolide	VSV	TS/A	PC3
275	Bonnet et al.	2013	Systemic delivery of sticky siRNAs targeting the cell cycle for lung tumor metastasis inhibition	J Control Release				research paper	GT	non viral carrier	siRNA	metastasis	TS/A	
276	De Medina et al.	2013	Dendrogenin A arises from cholesterol and histamine metabolism and shows cell differentiation and anti-tumour properties	Nat Commun	4	1840		research paper	PHARM	differentiation therapy	dendrogenin A	growth inhibition	TS/A	B16F10

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277	Dolinsek et al.	2013	Multiple Delivery of siRNA against Endoglin into Murine Mammary Adenocarcinoma Prevents Angiogenesis and Delays Tumor Growth	PLoS ONE	8	e58723		research paper	GT	gene silencing	endoglin	angiogenesis	TS/A	2H11
278	Hirsjarvi et al.	2013	Influence of size, surface coating and fine chemical composition on the in vitro reactivity and in vivo biodistribution of lipid nanocapsules versus lipid nanoemulsions in cancer models	Nanomed-Nanotechnol	9	375	387	research paper	IMAGING	targeting	lipid-based system	biodistribution	TS/A-pc	
279	Kamensek et al.	2013	Evaluation of p21 promoter for interleukin 12 radiation induced transcriptional targeting in a mouse tumor model	Mol Cancer	12	136		research paper	GT	radiation-induced transcriptional targeting	p21 promoter	growth inhibition	TS/A	
280	Kéramidas et al.	2013	The dual effect of mscs on tumour growth and tumour angiogenesis	Stem Cell Res Ther	4	41		research paper	BIOLMET	hMSCs	imaging	angiogenesis	TS/A	
281	Lollini et al.	2013	Preclinical vaccines against mammary carcinoma	Expert Rev Vaccines	12	1449	1463	review						
282	Lucá et al.	2013	The Fragile X Protein binds mRNAs involved in cancer progression and modulates metastasis formation	EMBO Mol Med	5	1523	1536	research paper	BIOLMET/GT	engineered cancer cells	FMRP	Metastasis	TS/A	4T1
283	Gravier et al.	2014	FRET Imaging Approaches for in Vitro and in Vivo Characterization of Synthetic Lipid Nanoparticles	Mol Pharmaceut	11	3133	3144	research paper	IMAGING	targeting	lipid-based system	FRET	TS/A-pc	
284	Longo et al.	2014	A general MRI-CEST ratiometric approach for pH imaging: Demonstration of in vivo pH mapping with iobitridol	J Am Chem Soc	136	14333	14336	research paper	IMAGING	magnetic resonance	Iobitridol	pH	TS/A	
285	Morris et al.	2014	Vaccination with tumor cells expressing IL-15 and IL-15Ralpha inhibits murine breast and prostate cancer	Gene Ther	21	393	401	research paper	TUMIMM/GT	engineered cancer vaccines	IL15	antitumor immunity	TS/A	TUBO, TRAMP C2
286	Bozon-Petitprin et al.	2015	Targeted radionuclide therapy with RAFT-RGD radiolabelled with (90)Y or (177)Lu in a mouse model of alphavbeta3-expressing tumours	Eur J Nucl Med Mol I	42	252	263	research paper	PHARM	radiotherapy	alphaVbeta3	growth inhibition	TS/A-pc	
287	Covre et al.	2015	Antitumor activity of epigenetic immunomodulation combined with CTLA-4 blockade in syngeneic mouse models	OncoImmunology	4	e1019978		research paper	TUMIMM	Epigenetic modulation	CTLA4	antitumor immunity	TS/A	
288	Delli Castelli et al.	2015	Sensitive MRI detection of internalized T<inf>1</inf>contrast agents using magnetization transfer contrast	NMR Biomed	28	1663	1670	research paper	IMAGING	magnetic resonance	MTC	in vivo imaging	TS/A	
289	Di Gregorio et al.	2015	An MRI Method to Map Tumor Hypoxia Using Red Blood Cells Loaded with a pO<inf>2</inf>-Responsive Gd-Agent	ACS Nano	9	8239	8248	research paper	IMAGING	magnetic resonance	hypoxia	in vivo imaging	TS/A	
290	Dolinsek et al.	2015	Endoglin silencing has significant antitumor effect on murine mammary adenocarcinoma mediated by vascular targeted effect	Curr Gene Ther	15	228	244	research paper	GT	gene silencing	endoglin	angiogenesis	TS/A	2H11
291	Mazzocco et al.	2015	Autologous cellular vaccine overcomes cancer immunoediting in a mouse model of myeloma	Immunology	146	33	49	citation						
292	Rizzitelli et al.	2015	Sonosensitive theranostic liposomes for preclinical in vivo MRI-guided visualization of doxorubicin release stimulated by pulsed low intensity non-focused ultrasound	J Control Release	202	21	30	research paper	IMAGING	magnetic resonance	lipid-based system	targeting	TS/A	
293	Stimac et al.	2015	Gene electrotransfer of plasmid with tissue specific promoter encoding shRNA against endoglin exerts antitumor efficacy against murine TS/A tumors by vascular targeted effects	PLoS ONE	10	e0124913		research paper	GT	gene silencing	endoglin	angiogenesis	TS/A	B16F1, B16F10, 2H11
294	Vannucci et al.	2015	In vivo targeting of cutaneous melanoma using an melanoma stimulating hormone-engineered human protein cage with fluorophore and magnetic resonance imaging tracers	J Biomed Nanotechnol	11	81	92	research paper	IMAGING	magnetic resonance	nanoparticles	drug delivery	TS/A	
295	Cottone et al.	2016	Leukocytes recruited by tumor-derived HMGB1 sustain peritoneal carcinomatosis	Oncoimmunology	5	e1122860		control model	BIOLMET/GT	inflammatory leukocytes	HMGB1	growth inhibition	TS/A	MC-38, CT26, C26, RMA
296	Falls et al.	2016	Murine tumor models for oncolytic rhabdo-virotherapy	ILAR Journal	57	73	85	review						
297	Karageorgis et al.	2016	An MRI-based classification scheme to predict passive access of 5 to 50-nm large nanoparticles to tumors	Sci Rep	6	21417		research paper	IMAGING	magnetic resonance	nanoparticles	targeting	TS/A-pc	
298	Longo et al.	2016	In Vivo Imaging of Tumor Metabolism and Acidosis by Combining PET and MRI-CEST pH Imaging	Cancer Res	76	6463	6470	research paper	IMAGING	magnetic resonance	PET	tumor metabolism	TS/A	
299	Longo et al.	2016	In Vitro and In Vivo Assessment of Nonionic Iodinated Radiographic Molecules as Chemical Exchange Saturation Transfer Magnetic Resonance Imaging Tumor Perfusion Agents	Invest Radiol	51	155	162	research paper	IMAGING	magnetic resonance	CEST	in vivo imaging	TS/A	

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300	Maru	2016	Whole-Body Matter	Inflamm Metast	12	1	505	review						
301	Prunier et al.	2016	LIM kinase inhibitor Pyr1 reduces the growth and metastatic load of breast cancers	Cancer Res	76	3541	3552	research paper	BIOLMET	LIM Kinase Inhibitor Pyr1	taxan	metastasis	TS/A	MEF
302	Riabov et al.	2016	Stabilin-1 is expressed in human breast cancer and supports tumor growth in mammary adenocarcinoma mouse model	Oncotarget	7	31097	31110	research paper	BIOLMET	TAM	stabilin1	growth inhibition	TS/A	
303	Rizzitelli et al.	2016	The release of Doxorubicin from liposomes monitored by MRI and triggered by a combination of US stimuli led to a complete tumor regression in a breast cancer mouse model	J Control Release	230	57	63	research paper	PHARM	magnetic resonance	doxorubicin	growth inhibition	TS/A	
304	Sandoval et al.	2016	Standardized Extract from Caesalpinia spinosa is Cytotoxic over Cancer Stem Cells and Enhance Anticancer Activity of Doxorubicin	Am J Chinese Med	44	1693	1717	research paper	PHARM	combination therapy	doxorubicin	chinese medicine	TS/A	B16, 4T1
305	Stimac et al.	2016	Tumor radiosensitization by gene therapy against endoglin	Cancer Gene Ther	23	214	220	research paper	GT	gene silencing	endoglin	angiogenesis	TS/A	
306	Anemone et al.	2017	In vivo evaluation of tumour acidosis for assessing the early metabolic response and onset of resistance to dichloroacetate by using magnetic resonance pHdichloroacetate by using magnetic resonance pH imaging	Int J Oncol	51	498	506	research paper	IMAGING	magnetic resonance	glycolytic phenotype	tumor metabolism	TS/A	
307	Anemone et al.	2017	MRI-CEST assessment of tumour perfusion using X-ray iodinated agents: comparison with a conventional Gd-based agent	Eur Radiol	27	2170	2179	research paper	IMAGING	magnetic resonance	CEST	tumor perfusion	TS/A	4T1
308	Cavallari et al.	2017	13C MR Hyperpolarization of Lactate by Using ParaHydrogen and Metabolic Transformation in Vitro	Chem-Eur J	23	1200	1204	research paper	IMAGING	metabolic transformation	ParaHydrogen	tumor metabolism	TS/A	
309	Fuchs et al.	2017	A combinatorial alpha-beta T cell receptor expressed by macrophages in the tumor microenvironment	Immunobiology	222	39	44	research paper	TUMIMM	TAM	TCRalpha/beta	antitumor immunity	TS/A	
310	Germano et al.	2017	Inactivation of DNA repair triggers neoantigen generation and impairs tumour growth	Nature	552	1	5	research paper	TUMIMM/GT	neoantigens	DNA repair	CRISPR	TS/A	CT26, MC38, PDAC
311	Hernández et al.	2017	A cytotoxic Petiveria alliacea dry extract induces ATP depletion and decreases β-F1-ATPase expression in breast cancer cells and promotes survival in tumor-bearing mice	Braz J Pharmacogn	27	306	314	research paper	PHARM	tumor metabolism	american traditional medicine	growth inhibition	TS/A	4T1, 3T3
312	Kurena et al.	2017	Magnetic nanoparticles for efficient cell transduction with SemlikiForest virus	J Virol Meth	245	28	34	research paper	GT	magnetofection	Semliki Forest viral vectors	in vitro gene therapy	TS/A	
313	Longo et al.	2017	EXCI-CEST: Exploiting pharmaceutical excipients as MRI-CEST contrast agents for tumor imaging	Int J Pharm	525	275	281	research paper	IMAGING	magnetic resonance	CEST	excipients	TS/A	B16-F10
314	Rong et al.	2017	Identifying tumor promoting genomic alterations in tumorassociated fibroblasts via retrovirus-insertional mutagenesis	Oncotarget	8	97231	97245	research paper	BIOLMET	TAF	insertional mutagenesis	tumor progression	TS/A	CT26, J558LFB-61, MCA-205
315	Vanpouille-Box et al.	2017	DNA exonuclease Trex1 regulates radiotherapy-induced tumour immunogenicity	Nat Commun	8	15618		research paper	TUMIMM	radiotherapy	abscopal effect	Trex1	TS/A	4T1, MCA38
316	Wang et al.	2017	Mammary adipocytes stimulate breast cancer invasion through metabolic remodeling of tumor cells	JCI Insight	2	e87489		research paper	BIOLMET	mammary adipocytes	microenvironment	metastasis	TS/A	
317	Yang et al.	2017	Immunocompetent mouse allograft models for development of therapies to target breast cancer metastasis.	Oncotarget	8	30621	30643	research paper	BIOLMET	murine mammary models	genomic profiling	metastasis	TS/A-E1	4T1, 6DT1, D2A1, E0771, MT6, F311, HRM-1, M6, Met-1, MVT1, r3T
318	Bauer et al.	2018	Blockade of Myeloid-Derived Suppressor Cell Expansion with All-Trans Retinoic Acid Increases the Efficacy of Antiangiogenic Therapy.	Cancer Res	78	3220	3232	research paper	TUMIMM	retinoids	MDSC	angiogenesis	TS/A	4T1
319	Bosnjak et al.	2018	Electrotransfer of different control plasmids elicits different antitumor effectiveness in B16.F10 melanoma	Cancers	10	E37		citation						
320	De Sanctis et al.	2018	Hyperthermic treatment at 56 degrees C induces tumour-specific immune protection in a mouse model of prostate cancer in both prophylactic and therapeutic immunization regimens	Vaccine	36	3708	3716	research paper	TUMIMM	hyperthermia	HMGB1	antitumor immunity	TS/A	TRAMP-C1, CT-26, C-51, N202.1A
321	Diamond et al.	2018	Exosomes Shuttle TREX1-Sensitive IFN-Stimulatory dsDNA from Irradiated Cancer Cells to DCs	Cancer Immunol Res	6	910	920	research paper	TUMIMM	exosomes	abscopal effect	Trex1	TS/A	A20, B16

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322	Groselj et al.	2018	Vascularization of the tumours affects the pharmacokinetics of bleomycin and the effectiveness of electrochemotherapy	Basic Clin Pharmacol Toxicol	123	247	256	research paper	PHARM	electrochemotherapy	Bleomycin	angiogenesis	TS/A	B16F1
323	McCaw et al.	2018	The expression of MHC class II molecules on murine breast tumors delays T-cell exhaustion, expands the T-cell repertoire, and slows tumor growth	Cancer Immunol Immunother	68	175	188	research paper	TUMIMM/GT	engineered cancer cells	CIITA	antitumor immunity	TS/A	
324	Ruggiero et al.	2018	Evidence for the Role of Intracellular Water Lifetime as a Tumour Biomarker Obtained by In Vivo Field-Cycling Relaxometry	Angew Chemie Int Ed	57	7468	7472	research paper	IMAGING	magnetic resonance	intracellular water	tumor biomarker	TS/A	4T1
325	Sasaki et al.	2018	Involvement of Prokineticin 2-expressing Neutrophil Infiltration in 5-Fluorouracil-induced Aggravation of Breast Cancer Metastasis to Lung.	Mol Cancer Ther	17	1515	1525	research paper	BIOLMET	infiltrating neutrophils	5-FU	tumor progression	TS/A	4T1
326	Savarin et al.	2018	Intravital Monitoring of Vasculature After Targeted Gene Therapy Alone or Combined With Tumor Irradiation	Technol Cancer Res Treat	17	1	8	research paper	GT	gene silencing	endoglin	angiogenesis	TS/A	
327	Soto-Mercado et al.	2018	TPEN exerts antitumor efficacy in murine mammary adenocarcinoma through an H2O2 signaling mechanism dependent on caspase-3	Anticancer Agents Med Chem	18	1617	1628	research paper	PHARM	caspase	TPEN	growth inhibition	TS/A	
328	Tran et al.	2018	Functionalization of Gadolinium Chelates Silica Nanoparticle through Silane Chemistry for Simultaneous MRI/(64)Cu PET Imaging	Contrast Media Mol Imaging	2018	7938267		research paper	IMAGING	magnetic resonance	nanoparticles	biodistribution	TS/A	
329	Witt et al.	2018	Cripto-1 Plasmid DNA Vaccination Targets Metastasis and Cancer Stem Cells in Murine Mammary Carcinoma	Cancer Immunol Res	6	1417	1425	research paper	TUMIMM/GT	DNA vaccine	Cripto1	metastasis	TS/A	TUBO, 4T1, D2F2
330	Znidar et al.	2018	Tumor cell death after electrotransfer of plasmid DNA is associated with cytosolic DNA sensor upregulation	Oncotarget	9	18665	18681	research paper	GT	electrotransfer	cytosolic DNA sensors	tumor cell death	TS/A	WEHI164
331	De Giovanni et al.	2019	Immune targeting of autocrine IGF2 hampers rhabdomyosarcoma growth and metastasis	BMC Cancer	19	126		citation						