Abstract. *L1 cell adhesion molecule (L1-CAM)* is a neuronal adhesion molecule which is expressed in many tumor entities. L1-CAM was shown to be involved in proliferation, invasion and metastasis both in vitro and in vivo. L1-CAM is engaged in homophilic interactions and complexes with many other ligands in a context-dependent manner. Activation and modulation of the extracellular signal-related kinase pathway by L1-CAM has been documented. In normal tissues, L1-CAM expression is restricted to nerve bundles and kidney tubules; however, L1-CAM is expressed in many tumor entities and, with the exception of neuroblastoma, L1-CAM expression correlates with poor prognosis. L1-CAM occurs in two isoforms, full-length L1-CAM and a variant in which exons 2 and 27 have been deleted. Preclinical experiments with available monoclonal antibodies are summarized and L1-CAM is analysed as a target for treatment of cancer with monoclonal antibodies.

In recent years, several monoclonal antibodies have been approved by the FDA for treatment of cancer. Among these are alemtuzumab (Campath) for treatment of chronic lymphocytic leukemia (CLL), bevacizumab (Avastin) for colon, lung cancer, glioblastoma and other types of cancer, cetuximab (Erbitux) for colon and head and neck cancer, panitumumab (Vectibix) for colon cancer, rituximab (Rituxan) for non-Hodgkin’s lymphoma and trastuzumab (Herceptin) for breast cancer. In addition, three conjugates have been approved: gemtuzumab (Mylotarg), an antibody-calicheamycin conjugate for acute myelogenous leukemia, and two radioisotope-conjugates of monoclonal antibodies, ibrutinumab (Zevalin) and tositumomab (Bexxar) for treatment of NHL. The attractive features of monoclonal antibodies are a documented increase of therapeutic benefit in comparison to standard of care therapy, especially in combination with chemotherapy, and favorable pharmacokinetic properties which allow administration schedules such as weekly or biweekly injections (1-3). With this class of biological therapeutics, common side-effects have been observed such as skin rashes, diarrhea, nausea, flu-like symptoms, allergic reactions and low blood counts which may lead to infections, bleeding and fever. But also more severe side-effects such as infusion reactions, heart failure and heart attacks have been reported.

Antibodies may interfere with the proliferation of tumor cells *in vitro* and *in vivo* and induce cell-cycle inhibition and apoptosis in tumor cells in which the antigen the antibody is directed against has an oncogenic function. In addition, depending on the isotype and the epitope, immune effector functions such as complement-dependent cytotoxicity and antibody-dependent cellular cytotoxicity can be exerted. In most therapeutic regimens antibodies are combined with chemotherapy or other drugs resulting in enhancement of efficacy.

Criteria for selection of transmembrane or membrane-associated targets for antibody-based therapy of cancer are: selectivity of antigen expression in normal versus tumor tissue, overexpression in tumors in comparison to matching normal tissues, involvement in tumorigenesis and maintenance of the transformed phenotype. In this context, we have summarized the features of the possible role of the adhesion-molecule L1-CAM for antibody-related therapy of cancer.

General Features of L1-CAM

L1-CAM is a member of the L1 family of adhesion molecules which are members of the immunoglobulin superfamily (IgSF CAMs). The members of the L1 family are L1-CAM (CD171), close homolog of L1-CAM (CHL1), neurofascin and NgCAM-related cell adhesion molecule (NR-CAM) (4-6). Amino acid sequence comparisons are shown in Figure 1. Between human L1-CAM and its paralogs NR-CAM, neurofascin and CHL1,
an amino acid homology of 40%, 39% and 40%, respectively, has been observed. The conserved exon-intron organization between human L1-CAM and its paralogues as shown in Figure 1 supports the assumption that they are derived from a primordial gene during evolution. They are found on neurons, especially on their axons and glial cells such as Schwann cells. L1-CAM is a neural cell adhesion molecule that is involved in the development of the central nervous system. Its topology and the amino acid sequences are shown in Figures 2 and 3. L1-CAM is composed of 28 exons and 27 introns and the molecular weight of its gene product ranges between 200 and 220 kDa (7). The extracellular domain consists of six Ig-like domains and five fibronectin-like domains (8, 9) and an N-glycosylation site is located in the first fibronectin domain. An RGD motif was identified in the first Ig-like domain. The transmembrane domain is located on exon 25 and the carboxyterminal cytoplasmic domain is encoded by exons 26, 27 and 28. Further features of the extracellular domain are homophilic binding and a homology region with FGFR. The cytoplasmic domain contains five potential phospho-serine-residue sites and can interact with the cytoskeleton, second messenger pathways and kinases (9-10). Two exons (2 and 27) are spliced alternatively (7, 10, 11). Figure 4 shows an amino acid alignment of human, rhesus monkey, rat, mouse, chicken, zebrafish and drosophila L1-CAM orthologs. The following percentage homologies have been noted: 99% human versus rhesus, 89% versus rat, 88% versus mouse, 49% versus chicken, 41% versus zebrafish and 30% versus drosophila. The number and location of the Ig-like and fibronectin-like domains are conserved between the species as outlined above. The RGD motif is conserved between the mammalian species shown in Figure 4 (human, rhesus monkey, rat and mouse).

L1-CAM is involved in axon guidance, neural cell migration and differentiation (10) and mutations in the gene cause X-linked neurological disorders known by the acronym CRASH (corpus callosum hypoplasia, retardation, adducted thumbs, spastic paraplegia and hydrocephalus) (11-13). The clinical picture resulting from L1-CAM mutations is extremely variable: more than 70 L1-CAM mutations have been described in all parts of the L1-CAM molecule in CRASH patients (11-13). L1-CAM knock-out mice show hyperplasia of the corticospinal tract and abnormalities of the ventricular system (14, 15). L1-CAM mediates adhesion to different substrates in a context-dependent manner (9). L1-CAM is involved in homophilic binding and was shown to interact with a plethora of adhesion molecules such as axonin-1/TAX-1, contactin, neurocan, neuropilin 1 and integrins such as αvβ3, α5β1, αvβ1 and αvβ5. Cis (between molecules in the same cell membrane) and trans (between molecules on opposing membranes) interactions have been described (9).

The extracellular domain of L1-CAM contains N-linked carbohydrates which can comprise up to 25% of the molecular weight of L1-CAM. Two sites of proteolytic cleavage have been identified in the extracellular domain of L1-CAM. Cleavage at the distal site mediated by the metalloprotease ADAM 10 results in fragments of 200 and 32 kDa (16, 17). Binding interactions of the cytoplasmic region of L1-CAM are reviewed elsewhere (18).

The L1-CAM isoforms are discussed separately in this paper. L1-CAM was shown to be involved in multiple proliferation-, anti-apoptosis- and angiogenesis-related pathways as outlined in Figure 5 and in the following parts of this review.

**L1-CAM Expression in Tumors and Assessment of L1-CAM as a Predictive Marker**

A gene expression data set derived from the Gene Expression Omnibus (GEO) database (GSE 2361) which compares 36 different normal human tissues indicates tissue-restricted expression of L1-CAM with a strong preference for expression in the brain as shown in Figure 6. In silico analysis of RNA transcripts for L1-CAM indicated strong overexpression of L1-CAM RNA in different subtypes of ovarian carcinoma (clear cell, endometroid, mucinous and serous) in comparison to normal ovarian tissue as shown in Figure 7A.

In a retrospective study comparing 58 ovarian carcinomas and 72 uterine adenocarcinomas, L1-CAM expression was identified as a marker for prediction of short survival (19). This finding fits with the hypothesis that L1-CAM expression and cleavage could promote dissemination of tumors by facilitating cell migration. The correlation as outlined above is independent of the tumor histotype. Monitoring of soluble L1-CAM during the follow-up period resulted in disease progression and recurrence being indicated before clinical symptoms were noted (19, 20). L1-CAM expression was correlated with disease progression even in stage I endometroid-type endometrial cases, identifying them as high-risk patients. In an independent study (21) of ovarian serous neoplasms (20 cystadenomas, 14 borderline tumors and 47 carcinomas), L1-CAM immunoreactivity significantly correlated with stage and grade. Sixty three carcinoma patients with low L1-CAM-expressing tumors exhibited a better response to chemotherapy and had a statistically longer progression-free survival. Differential roles of L1-CAM in ovarian carcinoma and ovarian surface epithelium have been proposed (18). It was shown that L1-CAM supports cell cell adhesion and enhances apoptosis in ovarian surface epithelial cells and has no effect on proliferation and invasion in this type of cell, whereas it inhibits adhesion and apoptosis in ovarian carcinoma cell lines (22). L1-CAM in a membrane-bound or soluble form was identified as a protector from apoptosis in ovarian carcinoma cells, whereas RNAi directed against L1-CAM sensitized cells to apoptosis induction. Cisplatin was shown to up-regulate L1-CAM expression in ovarian carcinoma (23).
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Figure 1. Comparison of amino acid sequences of members of the human L1-family. Sequences have been taken from Swiss-Prot (from top: L1CAM, NRRCAM, NFASC, and CHL) and annotated according to their gene structure as derived from the human genome. Identical amino acids, start of exons and RGD-motifs are specified by a color code as outlined.
Several studies have investigated the role of L1-CAM in progression of malignant melanoma. Comparison of the transcriptional profile of 45 primary melanomas, 18 benign skin nevi and seven normal skin specimen by Affymetrix microarray and confirmation by reverse-transcriptase-polymerase chain reaction (RT-PCR) analysis indicated L1-CAM as a marker to differentiate clinically relevant samples containing benign and malignant melanocytes (24). This finding was supported by a gene expression data set derived from the GEO database (GSE 3189) which points to a strong overexpression of L1-CAM in malignant melanoma compared to nevi and normal skin tissue, as shown in Figure 2B. Immunohistochemical (IHC) analysis of paraffin-embedded specimens of acquired melanocyte nevi, primary cutaneous melanomas and cutaneous and lymph node metastases of malignant melanomas revealed an increase in L1-CAM reactivity in malignant melanomas and metastases as compared to acquired melanocytic nevi. No expression of L1-CAM was detected in melanocytic nevi and melanocytes. Making use of melanoma cells from different stages of progression in monolayer and organotype human skin culture mimicking the pathophysiological environment of cutaneous melanoma, it was found that L1-CAM expression correlates with melanoma progression and αvβ3 integrin expression (25). Overexpression of L1-CAM in early radial growth phase melanoma cells promotes conversion from radial to vertical growth (25).

Analysis of L1-CAM immunoreactivity in 71 cases of pulmonary neuroendocrine tumors revealed that the percentage of L1-CAM expression increased with the aggressiveness and progression of the tumors, suggesting that L1-CAM immunoreactivity may be a useful diagnostic and prognostic marker in pulmonary neuroendocrine tumors (26). The tumors of 375 patients that underwent surgical treatment for colorectal cancer (CRC) were analyzed retrospectively for L1-CAM expression by IHC. L1-CAM was detected in 48 (13%) of patients. Analysis of L1-CAM expression and survival revealed a significantly worse outcome for L1-CAM-positive patients (27). In an independent study of 138 CRC patients who underwent surgery, L1-CAM expression was investigated in paraffin-embedded blocks of the tumors by tissue microarray analysis. Multivariate analysis revealed that L1-CAM was an independent prognostic marker for patient survival. L1-CAM expression was associated with tumor progression and poor survival in patients with CRC and may be clinically useful as a marker for poor prognosis (27). Additionally L1-CAM is associated with micrometastatic spread and poor outcome in CRC (28). L1-CAM expression was associated with the invasive front of colon tumors (29). Moreover, it was found to be highly expressed in gastrointestinal stromal tumors but not in smooth muscle tumors and desmoid-type fibromatosis (30). This may impact on differential diagnosis.

L1-CAM was found to be specifically expressed in poorly differentiated neuroendocrine pancreatic carcinomas that are known to have the worst prognosis (31). L1-CAM might be a marker for risk prediction in patients with pancreatic neuroendocrine carcinomas. Making use of two antibodies directed to the extracellular and the cytoplasmic domain, it was concluded that L1-CAM is expressed in renal cancer and correlates with metastases in clear cell carcinomas (32). Thirty-one neuroendocrine tumors of the skin (Merkel cell carcinoma) were investigated by IHC for L1-CAM expression (33); L1-CAM expression was detected in most of the tumors and staining was less frequent in metastases and recurrent tumors.

In contrast to tumors in adults where L1-CAM expression is associated with aggressive clinical behavior, expression of L1-CAM was correlated with favorable outcome in pediatric neuroblastomas (34) in a study in which L1-CAM expression was assessed on a tissue microarray with 66 surgically removed neuroblastomas by IHC and RT-PCR. The molecular basis for these findings have not yet been resolved.

Making use of monoclonal antibodies L1-11A and L1-14.10 revealed expression of L1-CAM in tumors of the female genital tract such as adenocarcinomas of the cervix and fallopian tubes, ovarian and endometrial carcinomas. Non-gynecological tumors expressing L1-CAM comprised malignant melanoma, colon cancer, clear-cell carcinomas of the urinary bladder, pheochromocytoma, small cell lung carcinoma, gastrointestinal tract carcinomas, gastrointestinal carcinoids, renal clear cell carcinomas, prostate adenocarcinomas and mesotheliomas (35). Further aspects of L1-CAM expression in cancer tissues have been reviewed recently (36).
Figure 3. Amino acid sequence, exon-intron organization and topology of human L1-CAM. The signal peptide, Ig-like domains, fibronectin-like domains, RGD motif and potential N-glycosylation site, transmembrane domain, potential phosphoserine residues, start of exons and exons 2 and 27 are shown by an appropriate color code.
L1-CAM Signaling and Cancer

L1-CAM and ADAM10 expression were shown to confer metastatic capacity of CRC cells to the liver and it was found that genes induced by L1-CAM in CRC cells are expressed at a higher level in tumor tissue than in normal tissue based on analysis of a large set of human CRC and normal tissue samples (36). L1-CAM was shown to be a target of β-catenin-Wnt signaling. Expression of L1-CAM confers cell motility, invasion and tumorigenesis in fibroblasts and colon cancer cells (16, 29, 36). In colorectal tumor tissue, L1-CAM was exclusively localized at the invasive front of the tumor tissue that expresses nuclear β-catenin together with ADAM10 that is involved in cleavage and shedding of the L1-CAM extracellular domain (29). Homophilic and heterophilic L1-CAM binding and concomitant signaling has been shown to promote cell motility. L1-CAM induces and maintains a motile and invasive phenotype by inducing transcription of corresponding genes. In the presence of serum or platelet-derived growth factor, L1-CAM was shown to stimulate the extracellular signal-related kinase (ERK) pathway. Activation of this pathway leads to expression of motility- and invasion-related gene products such as β3 integrin subunit, small GTPases and cysteine proteases cathepsin-L and -B (37-40). In the context of a genetic screening, L1-CAM together with cell surface targets IGF2R and SCL31A1 were identified as survival factors which protect tumor cells such as HCT 116 colon carcinoma cells.
Figure 4. Comparative amino acid sequences of L1-CAMs from different species. Sequences have been taken from UniProt and RefSeq (from top: SW: L1CAM_HUMAN, RSP:XP_001087861, SW: L1CAM_RAT, SW: L1CAM_MOUSE, SW: L1CAM_CHICK, TR:B3DGN9_DANRE, SW: NRG_DROME) and annotated according to L1CAM_HUMAN. Identical amino acids, Ig-like domains, transmembrane domain, exon 2 and 27 and RGD motifs are boxed and/or highlighted by specified color code.
from apoptosis (41). These findings were supported by the fact that RNAi directed against L1-CAM was shown to induce apoptosis in HCT 116 cells.

The role of L1-CAM in cell migration is probably cell type and context dependent. L1-CAM-dependent up-regulation of αvβ3 integrin involving activation of ERK was described. However, it was shown that L1-CAM and αvβ3 are not co-expressed in ovarian carcinoma. Overexpression of L1-CAM did not up-regulate αvβ3 in ovarian carcinoma cells, but was able to do so in HEK 293 cells (42). The binding of L1-CAM on ovarian carcinoma cell lines to neuropilin-1 on mesothelial cells which form the lining of the peritoneum was demonstrated. Likewise, soluble L1-CAM also binds to neuropilin-1. This interaction may contribute to growth of ovarian carcinomas and to reciprocal signaling between mesothelial cells and tumors (43).

In line with the function of L1-CAM as a mediator of the epithelial-mesenchymal transition effects are findings in breast carcinoma MCF-7 cells which express the non-neuronal isoform of L1-CAM. Knock-down of L1-CAM revealed that L1-CAM expression leads to disruption of adherens junctions and increases β-catenin transcriptional activity. Expression of the non-neuronal isoform of L1-CAM was found in 16 out of 17 tumor cell lines originating from different tumor types (44).

The C-terminal fragment of L1-CAM is translocated to the nucleus and is involved in L1-CAM-dependent gene regulation (37). Full-length L1-CAM has to undergo sequential cleavage by ADAM 10 and presenilin/γ secretase in order to reach the nucleus. It was shown that the RGD binding site located in the sixth Ig domain of L1-CAM is important for nuclear signaling (40). The corresponding mutant protein was unable to translocate to the nucleus. Shedding of L1-CAM and its physiological consequences has been investigated (36). As outlined, soluble L1-CAM is produced by metalloproteinase-mediated ectodomain shedding of L1-CAM. In addition, it was shown that hepatocyte growth factor (HGF) mediates release of a 180 kDa form of L1-CAM into the media of renal carcinoma cells in a dose-dependent manner (45). Making use of L1-CAM mutants, it was demonstrated that the cytoplasmic domain of L1-CAM regulates basal shedding and association with the cytoskeleton through the ankyrin binding site is involved in shedding. Constitutive cleavage of L1-CAM can occur in exosomes as shown in ovarian carcinoma cell lines (46). Constitutive cleavage is mediated by ADAM 10, a disintegrin and metalloproteinase 10. Exosomes are continuously released from the cells and can be found in the ascites fluid and serum of ovarian cancer patients. It was shown that soluble L1-CAM (sL1-CAM) is a mediator of angiogenesis probably due to ligation of integrins based on interaction with the RGD motif (47). The angiogenic activity of sL1-CAM could be abolished by a chimeric antibody directed against L1-CAM, chCE7. sL1-CAM induced proliferation, matrigel invasion and tube formation of bovine aortic endothelial cells and revealed proangiogenic activity in the chick chorioallantoic membrane assay. sL1-CAM is a ligand for several integrins and can be deposited in the extracellular matrix.

Another important issue of L1-CAM is its involvement in chemoresistance (apoptosis resistance). It was found by making use of L1-transfectants that ovarian carcinoma cells expressing L1-CAM are more resistant to apoptosis (48). Treatment with apoptotic stimuli up-regulated the anti-apoptotic molecule Bcl-2 to a greater extent in HEK 293 cells expressing L1-CAM. In HEK-293 cells, L1-CAM mediates ERK, FAK and PAK phosphorylation. Selection of m130 ovarian carcinoma or SW 207 colon carcinoma cells with cisplatin leads to up-regulated expression of L1-CAM. In the ovarian carcinoma cell line OVMZ, knock-down of L1-CAM by RNAi sensitized cells to apoptosis induction. Similar findings of drug-induced expression of L1-CAM conferring anti-apoptotic protection and chemoresistance were described for pancreatic ductal adenocarcinoma cells (PT 45-P1 res cells) (49). L1-CAM knock-down by RNAi in this cell line led to an increase of anticancer drug-induced caspase activation. Conversely, overexpression of L1-CAM in PT 45-P1 cells conferred anti-apoptotic protection against anticancer drug treatment. IHC analysis revealed expression of L1-CAM in 80% of pancreatic adenocarcinomas.

### L1-CAM Splice Variants

L1-CAM is normally found in neural tissue, whereas non-neural cells including cancer cells, predominantly express the variant lacking exons 2 and 27 (50-55). The biological functions of exons 2 and 27 have been studied in the nervous system. Exon 2 is important for homophilic L1-L1 binding...
**Antibodies Directed against L1-CAM**

Anti-neuroblastoma antibody chCE7 was shown to bind to L1-CAM on renal carcinoma cells and is internalized by human neuroblastoma cells (64, 65). It was found that chCE7 binds near to the sixth Ig-like domain of human L1-CAM, which contains a single RGD sequence. L1-CAM antibodies chCE7 and L1-11A inhibit proliferation of ovarian carcinoma SKOV3ip cells and other L1-CAM-positive tumor cells (renal, neuroblastoma, colon) (66, 67). For two other cell lines, cross-linking with a secondary antibody was necessary for significant inhibition of proliferation by L1-11A, but not by chCE7. Biweekly treatment of ovarian carcinoma-bearing mice with L1-11A led to a dose-dependent and significant reduction of tumor burden (up to 63.5%) and ascites formation (up to 75%) (68). Genistein potentiates the anti-proliferative and pro-apoptotic effects of chCE7 in SKOV3ip cells (69). This was reflected by reduction of the sensitivity of p44/42 (ERK1, 2) kinase, src and Akt to stimulation with serum, EGF and HGF. L1-CAM augments tumor growth and invasion due to induction of ERK-dependent genes and this effect can be inhibited by monoclonal antibodies directed against L1-CAM.
Mutation of L1-CAM in the cytoplasmic domain (T1274A, S1248A) abrogates ERK activation and blocks cell migration on extracellular matrix proteins (37, 70). These mutations did not augment tumor growth in NOD/SCID mice. Induction of ERK-dependent genes such as β3 integrin, cathepsin-B and several transcription factors and the invasive phenotype were abrogated. Due to the restricted expression of L1-CAM outside the nervous system, monoclonal antibodies and antibody fragments armed with radio-isotopes were evaluated in preclinical radioimmunotherapy approaches (71, 72). For 177Lu-DOTA-labeled aglycosylated L1-CAM antibody chCE7, the influence of the number of chelators on in vitro and in vivo properties such as elimination in the blood and uptake in the liver were investigated (73). The highest specific activity was obtained with a chelator-to-antibody ratio of 12. 67Cu conjugated with chCE7 was evaluated with respect to therapeutic efficacy in orthotopically implanted SKOV-3ip in nude mice. Two mutations were introduced to achieve more rapid blood clearance. Tumor growth inhibition and increase in survival was shown. A combination of unlabeled antibody L1-11A with a subtherapeutic dose of 67Cu radioimmunotherapy also prolonged survival significantly (74). 177Lu and 67/64Cu-labeled F(ab')2 fragments of chCE7 were evaluated as imaging agents in L1-CAM-positive xenografts. 131Iodine-labeled chCE7 was successfully evaluated for tumor imaging in patients with recurrent neuroblastoma (75).

L1-CAM Antibodies for Treatment of Cancer

As outlined in the preceding sections, L1-CAM is expressed in many types of tumors. In normal tissues, L1-CAM was detected in peripheral nerve bundles and in the collecting tubules of the kidney (31). Therefore the assessment of the toxicology profile of therapy-related L1-CAM antibodies in cross-reacting species is an important issue. Albeit functional domains of the extracellular domain of L1-CAM have been mapped, a systematic study for evaluation of in vitro and in vivo properties of L1-CAM antibodies directed against different epitopes is still pending. It is reasonable to predict that defined properties of L1-CAM antibodies will be correlated with defined epitopes. Some of the described antibodies were shown to interfere or modulate ERK signaling and thus impact on invasion and proliferation. Inhibition of proliferation of selected tumor cell lines by L1-CAM monoclonal antibodies in the absence of immune effector cells has been shown. The molecular details of these findings, correlation with L1-CAM density on the cell lines, dependency of efficacy on internalization of antigen-antibody complexes and extension to a broader panel of tumor cell lines should be explored in more detail. In addition, transcriptional profiling and proteomics-based analysis of L1-CAM monoclonal antibodies in responding and non-responding tumor cell lines would help to resolve issues such as cell type- and context-dependent in vitro and in vivo efficacy. In vivo efficacy studies have focused on inhibition of invasion and metastasis by L1-CAM monoclonal antibodies (68). The impact of such antibodies on the growth of established xenografts derived from a broad panel of tumor cell lines should be investigated in more detail to come up with a clearer picture of their role in the context of tumor growth inhibition.

The function of the two L1-CAM isoforms in cancer biology, such as their impact on proliferation, differential interaction with ligands, and involvement in migration and invasion, should be explored in more detail in order to design antibodies directed against L1-CAM with optimized efficacy. The generation of monoclonal antibodies selective for each of the two isoforms would allow the IHC profiling of primary tumors and metastatic lesions with respect to the expression of the L1-CAM isoforms. In this context, analysis of matching primary tumors and corresponding metastases might impact on treatment strategies. In addition to therapy of defined tumor entities with L1-CAM monoclonal antibodies, different treatment strategies such as conjugates between the antibodies and cytotoxics, vaccination against non-neuronal epitopes of L1-CAM and treatment of patients with educated T-cells directed against L1-CAM-expressing tumor cells (76) might be explored further.
References


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