Cancer vaccines for patients with acute myeloid leukemia – definition of leukemia-associated antigens and current clinical protocols targeting these antigens

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Targeted immunotherapies require the identification and characterization of appropriate antigen structures. Initially, T-cell based cancer vaccines were designed for patients with solid tumors after the definition of suitable tumor-associated antigens. Several immunological and even clinical responses prompted researchers and clinicians to extend the spectrum of cancer vaccines towards hematologic malignancies such as acute myeloid leukemia (AML). Only 20-40% of all patients with AML achieve a disease-free survival of more than 5 years. The graft-versus-leukemia (GVL) effect observed after allogeneic stem cell transplantation and donor lymphocyte infusions strongly suggests that T lymphocytes play a major role in the rejection of leukemic cells. Therefore, immunotherapy directed against leukemia-associated antigens might elicit specific immune responses that could eliminate minimal residual disease after chemotherapy, or enhance the GVL effect after hematopoietic stem cell transplantation. This review summarizes hitherto identified and characterized LAA as targets for T-cell-based immunotherapies. Current clinical peptide vaccination trials targeting different epitopes of the Wilms’ tumor gene 1 (WT1), the proteinase-3 derived epitope peptide (PR1) and the receptor for hyaluronic acid mediated motility (RHAMM/CD168) derived epitope R3 are reviewed, and perspectives but also limitations of immunotherapeutic approaches for AML patients are discussed.

Key words: acute myeloid leukemia (AML), cancer vaccines, leukemia-associated antigens (LAA), peptide vaccination, dendritic cells (DC).

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Immunotherapeutic approaches for patients with acute myeloid leukemia

Sixty to eighty percent of patients with acute myeloid leukemia (AML) younger than 60 years achieve a complete remission after polychemotherapy or stem cell transplantation.1 In elderly patients with AML, the rate of complete remissions is markedly reduced;2 AML patients often relapse and the 5-year survival rate of all patients with AML is rather poor, being 20-40%.1 Given the prognosis of AML patients, there is a fervent need for novel therapies that could reduce the risk of relapse after chemotherapy or stem cell transplantation by eliminating residual leukemic cells, i.e. minimal residual disease. Eradication of such residual leukemic cells after allogeneic stem cell transplantation using donor lymphocyte infusions3,4 provides strong evidence for the efficient action of T lymphocytes against leukemic cells which express major histocompatibility (MHC) class I and class II molecules and the co-stimulatory molecule CD80.5 The development of more leukemia-specific T-cell therapies for AML patients depends on the molecular definition of immunogenic leukemia-associated antigens (LAA) that are specifically recognized by the immune system.6

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Chen et al. identified a RHAMM/CD168-like protein that induced serological immune responses in 70% of AML patients, but not in healthy volunteers. 13 For RHAMM/CD168, we characterized the naturally processed peptide RHAMM/CD168-R3 as an epitope inducing specific immune responses by CD8+ early effector T cells. 14 Lysis of autologous AML blasts, dendritic cells generated from autologous AML blasts and RHAMM/CD168-R3-pulsed T2 cells was restricted to major histocompatibility complex class I molecules and was epitope-specific as demonstrated in antibody-blocking and cross-priming experiments. 14, 15 In addition to these antigens newly identified in AML patients, various different tumor-associated antigens already characterized in solid tumors or other hematologic malignancies have been reported to induce immune responses in patients with AML. Proteinase 3 is a synonym for the anti-nuclear cytoplasmatic antigen (ANCA) which is known to be immunogenic in Wegener’s granulomatosis. A CTL peptide-epitope, designated PR1, has been shown to induce specific immune responses in HLA-A*0201 positive patients with CML or AML. 16 Molldrem et al. characterized these immune responses as mediated by high affinity CD8+ T lymphocytes. 27 A phase I/II clinical peptide vaccination trial has already been initiated for HLA-A*0201 positive patients with myelodysplastic syndrome, AML or CML, and immunological and clinical responses could be measured in these vaccinated patients. 16 The Wilms’ tumor gene 1 (WT1), a differentiation gene, is expressed in most AML patients, 19, 20 but also in CD34 positive cells of early normal hematopoiesis; its expression in patients with AML is correlated with a poor clinical prognosis. 21, 22 Specific CD8+ T-cell responses against WT1-derived peptides could be detected in HLA-A*024 and HLA-A*0201 positive patients with AML. 23 Elisseeva et al. showed that humoral immune responses against the WT1 protein, could be elicited in patients with WT1-expressing malignancies: 3/18 AML patients showed serological immune responses against WT1, as detected by enzyme linked immunosorbent assays. 24 Ikeda et al. showed that the TAA PRAME is a melanoma-associated antigen recognized by CTL in a HLA-A*024-restricted manner. 25 PRAME is a dominant repressor of retinoic acid receptor (RAR) signaling and it binds to RAR in the presence of retinoic acid, thus preventing ligand-induced receptor activation and target gene transcription. 26 Different peptides inducing specific immune responses of CD8+ T cells were characterized in HLA-A*0201 positive patients with AML. 27 No serological immune responses to PRAME have been described up to now.

Dendritic cells expressing the oncofetal antigen-immature laminin receptor (OFA-iLRP) have induced specific CD8+ T cells. 28 Siegel et al. described the lysis of OFA-iLRP-expressing AML cells but not of normal cells of healthy volunteers. 28 It has been demonstrated in murine and human studies that OFA-iLRP is an immunogenic protein that specifically induces T cells of patients with AML 29–31 and various solid tumors. 29 BCL-2 is another antigen inducing specific T-cell responses in AML patients. BCL-2 plays an important role in the regulation of apoptosis. Andersen et al. described spontaneous immune responses of specific CTL against BCL-2 in patients with AML, but not in healthy volunteers. 28 Antibody-directed immune responses have not hitherto been described for either OFA-iLRP or BCL-2.

Using the SEREX approach, high titer antibody responses to the leukemia-associated antigens CML 28 and CML 66 were detected in patients with CML. These immunoglobulin G responses against these two antigens showed a correlation with immune-induced remission by donor lymphocyte infusion. 29 Both CML28 and CML66 were highly expressed in leukemic blasts from patients with AML and CML in blast crisis, but not in normal peripheral blood or most bone-marrow cells. 30, 31 CD34+ hematopoietic progenitor cells showed a low level of expression of these antigens. 29 Recently, HLA-A*0201-restricted specific T-cell responses against CML28 were described in healthy volunteers 32 and CML patients. Survivin inhibits apoptosis and is expressed in several human cancers and hematologic malignancies but not in most differentiated normal adult tissue. 33 Leukemic cells of AML patients express survivin, and responses by specific CD8+ T cells were found in cancers and recently also in AML patients. 34, 35 Due to its cancer-related expression, survivin is a promising target for specific immunotherapies. Survivin expression was associated with a shorter overall survival in childhood AML but non in adult AML patients. 35 A characteristic finding in about 50% of AML cases is the presence of chromosomal translocations resulting in generation of tumor-specific

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fusion products. Over 95% of CML patients express the fusion product \textit{bcr-abl} that could induce specific T-cell responses.\textsuperscript{40} Such tumor-specific products might consitute appropriate structures for immunotherapeutic approaches also in patients with AML. However, as of present only a few fusion products inducing specific immune responses in AML patients have been identified. One fusion protein that induces immune responses in AML patients is \textit{DEK-CAN}, a product derived from the \textit{t(6;9)} translocation. A CD4\textsuperscript{+} cell line was shown to kill B cells pulsed with peptides derived from the breakpoint region of this fusion molecule.\textsuperscript{43} However, this molecular event is rare in AML patients and no cellular immune response of CD8\textsuperscript{+} T cells has been demonstrated. Osman et al. showed activation of CD4\textsuperscript{+} and CD8\textsuperscript{+} T cells by dendritic cells pulsed with a peptide derived from the \textit{PML-RARA} fusion product present in acute promyelocytic leukemia.\textsuperscript{44} Maeda et al. were able to induce HLA-A*0201-restricted CTL lines against an MTG8-derived peptide using monocyte-derived dendritic cells from a healthy donor.\textsuperscript{45} The fusion protein AML-MTG8 might, therefore, be an interesting target in (8;21) positive AML as it is expressed in about 20% of patients with AML. Nevertheless, further experiments investigating the specificity, frequency and natural processing of this potential antigen need to be performed.

### Table 2. Differential expression of various LAA in AML, normal tissue and normal CD34\textsuperscript{+} hematopoietic progenitor cells.

<table>
<thead>
<tr>
<th>LAA</th>
<th>Gene function</th>
<th>Expression frequency in AML</th>
<th>Expression in other hematological malignancies</th>
<th>Expression in solid tumors</th>
<th>Expression in normal tissue</th>
<th>Expression in normal CD34\textsuperscript{+} stem cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>BAGE</td>
<td>Related to hypomethylation\textsuperscript{45}</td>
<td>27%</td>
<td>CML: 4%\textsuperscript{46}</td>
<td>Various solid tumors\textsuperscript{47}</td>
<td>CT antigens\textsuperscript{48,49}</td>
<td>No expression\textsuperscript{50}</td>
</tr>
<tr>
<td>BCL-2</td>
<td>Oncogene, inhibition\textsuperscript{51}</td>
<td>84%</td>
<td>High expression of a apoptosis\textsuperscript{52} in different hematologic malignancies\textsuperscript{53}</td>
<td>Various solid tumors\textsuperscript{54}</td>
<td>In different normal tissues\textsuperscript{55}</td>
<td>Positive\textsuperscript{56}</td>
</tr>
<tr>
<td>CML28</td>
<td>Component of human exosome, involved in processing and degradation of RNA\textsuperscript{57}</td>
<td>89%</td>
<td>CML\textsuperscript{58,59}, RCC\textsuperscript{60}, head and neck,\textsuperscript{61} NSCLC\textsuperscript{62}</td>
<td>Various solid tumors\textsuperscript{63}</td>
<td>No expression except testis\textsuperscript{64}</td>
<td>Positive\textsuperscript{65}</td>
</tr>
<tr>
<td>G250/CA9</td>
<td>Hypoxia regulated gene\textsuperscript{66}</td>
<td>51%</td>
<td>Unknown</td>
<td>RCC,\textsuperscript{67} head and neck,\textsuperscript{68} NSCLC\textsuperscript{69}</td>
<td>No expression\textsuperscript{70,71}</td>
<td>No expression\textsuperscript{72}</td>
</tr>
<tr>
<td>HAGE</td>
<td>Unknown\textsuperscript{73}</td>
<td>23%</td>
<td>CML: 54%\textsuperscript{74}</td>
<td>Various solid tumors\textsuperscript{75}</td>
<td>testis, placenta and pancreas\textsuperscript{76}</td>
<td>Unknown</td>
</tr>
<tr>
<td>hTERT</td>
<td>Catalytic subunit of the telomerase gene, activation of telomerase activity\textsuperscript{77}</td>
<td>28%</td>
<td>CML: 59%,\textsuperscript{78} CL: 53%</td>
<td>Various solid tumors\textsuperscript{79}</td>
<td>No expression\textsuperscript{80}</td>
<td>Positive,\textsuperscript{81} negative\textsuperscript{82}</td>
</tr>
<tr>
<td>MPP11</td>
<td>M-phase phosphoprotein 11, cell proliferation\textsuperscript{83}</td>
<td>86%</td>
<td>CML: 90%,\textsuperscript{84} CL: 13%\textsuperscript{85}</td>
<td>Various solid tumors\textsuperscript{86}</td>
<td>Testis, low expression in kidney and lung\textsuperscript{87}</td>
<td>17%\textsuperscript{88}</td>
</tr>
<tr>
<td>OFA-ILRP</td>
<td>Oncofetal protein, receptor for uptake protein into cells\textsuperscript{89}</td>
<td>100%</td>
<td>CLL, ALL, CML\textsuperscript{90}</td>
<td>Various solid tumors\textsuperscript{91}</td>
<td>No expression\textsuperscript{92,93}</td>
<td>No expression\textsuperscript{94}</td>
</tr>
<tr>
<td>PRAME</td>
<td>Controversial repressor of retinoid acid,\textsuperscript{95} induction of apoptosis\textsuperscript{96}</td>
<td>64%\textsuperscript{97,98}</td>
<td>CML: 62%,\textsuperscript{99} CL: 3%\textsuperscript{100} ALL: 42%\textsuperscript{101}</td>
<td>Various solid tumors\textsuperscript{102}</td>
<td>Testis, placenta, ovary, pancreas\textsuperscript{103}</td>
<td>No expression\textsuperscript{104}</td>
</tr>
<tr>
<td>PR3</td>
<td>Neutrophil serine elastase, IL-32 binding protein\textsuperscript{105}</td>
<td>67%\textsuperscript{106,107}</td>
<td>CML\textsuperscript{108,109}</td>
<td>Not in solid tumors\textsuperscript{110}</td>
<td>Myeloid cells\textsuperscript{111} and normal tissues\textsuperscript{112}</td>
<td>Positive\textsuperscript{113,114}</td>
</tr>
<tr>
<td>RHAMM</td>
<td>Formation of mitotic spindle, signal transduction\textsuperscript{115}</td>
<td>70%\textsuperscript{116,117}</td>
<td>AML, MDS, MM, CML\textsuperscript{118,119,120}</td>
<td>Ovarian carcinoma, RCC, breast cancer, melanoma\textsuperscript{121}</td>
<td>Testis, thymus, placenta\textsuperscript{122}</td>
<td>No expression,\textsuperscript{123} positive in mobilized SC\textsuperscript{124}</td>
</tr>
<tr>
<td>Survivin</td>
<td>Inhibition of apoptosis\textsuperscript{125}</td>
<td>100%</td>
<td>CML\textsuperscript{126}, Different lymphomas, CML\textsuperscript{127}, MM\textsuperscript{128}</td>
<td>Various solid tumors\textsuperscript{129}</td>
<td>Not in normal differentiated tissues\textsuperscript{130,131}</td>
<td>Positive\textsuperscript{132}</td>
</tr>
<tr>
<td>WT-1</td>
<td>Transcription factor\textsuperscript{133}</td>
<td>67%\textsuperscript{134,135}</td>
<td>AML, MDS, CML\textsuperscript{136,137,138}</td>
<td>Various solid tumors\textsuperscript{139,140}</td>
<td>Only placenta\textsuperscript{141}</td>
<td>Positive\textsuperscript{142,143}</td>
</tr>
</tbody>
</table>

\textit{CT} gene: gene only expressed in cancer tissue and tests; RCC: renal cell carcinoma; NSCLC: non-small cell lung cancer.
Cancer/testis antigens are antigens which are only expressed in cancer cells and in testis/germline cells. Different immunogenic antigens characterized in solid tumors or leukemias are expressed in AML cells and are listed in the Table 2. AML is a clonal disorder of the hematopoietic system, therefore the homogeneity of the LAA expression is high, especially when compared with LAA expression in CML.

**Immunotherapeutic approaches in AML**

**Cytokines and donor lymphocyte infusion**

The immune system plays an important role in the control of malignant/leukemic cells. Different rather unspecific therapies have been employed to stimulate the immune system against AML blasts: interleukin-2, a cytokine for T-cell stimulation, induced clinical remissions in AML patients. Additionally, interferon-α induces long-term remissions in CML patients and this effect might be induced by specific stimulation of the immune system against LAA. Grigg et al. described the use of interferon-α to promote graft-versus-host disease (GVHD) after allogeneic bone marrow transplantation and to enhance the graft-versus-leukemia (GVL) effect observed after donor lymphocyte infusion. For younger patients with AML and CML, allogeneic stem cell transplantation is a curative treatment option. This approach exploits the effects of total body irradiation and chemotherapy, but also the induction of the GVL effect. In case of relapse or minimal residual disease, the infusion of donor lymphocytes is a therapeutic option to induce anti-leukemia effects. These immunological effects demonstrate the potential of donor lymphocytes to reject malignant cells and suggest that LAA are recognized by these donor lymphocytes.

**Peptide vaccination trials in AML**

LAA-derived T-cell epitope peptides can be administered into the skin where they are potentially taken up by antigen presenting cells forming the immunological synapses with T cells in locoregional lymph nodes. Such vaccination might result in an enhanced T-cell response against leukemic cells (Figure 1). Various peptides derived from LAA are under clinical investigation for AML patients in current peptide vaccination trials: (i) the proteinase 3-derived peptide, PR1; (ii) WT1-derived peptides (iii) the RHAMM/CD168-derived peptide, R3.

Data from these peptide vaccination trials are summarized in Table 3: (i) The proteinase 3-derived peptide, PR1, has been investigated in a phase I/II study. The HLA-A*0201-restricted CD8+ T-cell epitope peptide PR1 has been combined with incomplete Freund’s adjuvant and granulocyte-monocyte colony-stimulating factor and administered every three weeks for a total of 3 vaccinations. Patients with AML, CML and MDS were included in this study. Specific immunological responses were observed in more than 50% of patients and clinical responses were also detected. Vaccine-induced PR1-specific CD8+ T cells with high avidity were measured by αβ-chain mutant tetramers. The frequency of these T cells seemed to be predictive of the clinical responses of the patients to the peptide vaccination. (ii) Phase I/II peptide vaccination trials have been performed for patients with AML, CML and MDS using Wilms’ tumor gene 1.

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### Figure 1. Peptide vaccination of patients with AML. Therapeutic vaccination with a peptide consists in the subcutaneous injection of the peptide into the thigh in the vicinity of loco-regional lymph nodes of an AML patient. The injected exogenous peptide can bind to a class I molecule of the major histocompatibility complex (MHC) of an antigen presenting cell (APC) such as a Langerhans’ cell and is presented to a naive CD8+ T lymphocyte migrating to the next lymph node (upper panel). The nucleus of an AML blast contains DNA encoding a specific leukemia-associated antigen (LAA), which is translated and digested in the proteasome (lower panel). Subsequently, the antigen is processed in the MHC class I pathway and eventually presented on the surface of the AML blast by a class I molecule of the MHC. Thus, the presented peptide in the groove of the MHC class I molecule can fit the T-cell receptor (TCR) of a lymphocyte which has been activated in the way indicated in the upper part of the cartoon presenting the same T-cell epitope peptide derived from the LAA. In this case, the T-cell docks again on the MHC class I molecule with the LAA epitope peptide, resulting in release of granzyme B, perforin and FasL leading to the lysis of the AML blast. This is the aim of immune therapy for AML using a defined T-cell epitope peptide derived from a LAA.
Cancervaccines for AML patients

(WT1) 23, 90-derived peptides matching HLA-A2 or HLA-A24. Recently, Mailander et al. described the induction of a complete remission in an HLA-A2 patient vaccinated with a WT1 peptide. Scheibenbogen reported on the vaccination of HLA-A2 patients. One patient in partial remission achieved a complete remission after vaccination; two others maintained their complete remission. Nine patients with progressive disease remained stable or progressed further. Oka et al. described a phase I study using an HLA-A24-restricted peptide for patients with breast cancer, lung cancer, AML and MDS. Peptide derived from WT1 was also emulsified with the incomplete Freund’s adjuvant. Twelve out of a total of 25 patients were AML patients in complete remission and remained in complete remission during the peptide vaccination. Clinical responses in patients with other types of tumors could be correlated to the increase of WT1-specific immune responses. (iii) For the cell-surface antigen RHAMM/CD168, 14, 93 a phase I/II peptide vaccination trial using the HLA-A2-restricted RHAMM/CD168-R3-peptide was initiated in patients with AML, MDS and multiple myeloma. In vitro experiments showed specific T-cell responses from CD8+ early effector T cells against RHAMM/CD168 in AML patients. RHAMM/CD168 is a naturally processed antigen that is highly expressed in the majority of patients with AML, CML and multiple myeloma, but also in those with different solid tumors. Ten patients suffering from AML, MDS or multiple myeloma were vaccinated with the RHAMM/CD168-R3 peptide. Five of these ten patients showed immunological responses; among the three patients with AML, one achieved complete remission having been in partial remission, one remained stable, and one had progressive disease. Vaccination strategies using peptides in patients with hematologic malignancies were shown to be safe, confirming the experience in patients with solid tumors, and specific immune responses could be detected. Therefore, the search for the best peptides, the optimal conditions and also appropriate adjuvants must be continued once the results from all patients in these studies have been fully evaluated.

### Potential limitations of immunotherapy in AML

T cells play an important role in the immune defense against solid tumors and hematologic malignancies; however, there are mechanisms that might hamper tumor control by T lymphocytes, e.g. therapy-related immune defects, loss of MHC class I molecules, immunosuppressive factors secreted by cancer cells, direct tumor cell/T-cell interactions and induction of regulatory T cells.

### Immune defects in AML patients

Chemotherapeutic approaches might induce cytopenia in the peripheral blood as well as in the bone marrow, but
their effect on T-cell function is not clear. Wendelbo et al. described a dose-dependent effect on T cells.49 myeloma patients with post-transplant cytopenia have a more severe cellular immune deficiency than patients treated with conventional chemotherapy. However, several studies showed that circulating T cells detected early after chemotherapy are functional.50-57 The memory T-cell compartment in particular is less affected by chemotherapy and even by stem cell transplantation approaches in leukemia patients.58-64 Moreover, Wendelbo et al. showed that the proliferation of T cells of AML patients increased after intensive chemotherapy and that these cells are effector cells for specific immunotherapeutic approaches in AML.65 Recently, our group demonstrated that AML patients with expression of at least one of the LAA, RHAMM, FRAME or G250 on their leukemic blasts had a significant improvement of overall survival.54 This positive effect might result from sufficient stimulation of the immune system to eliminate cells of minimal residual AML cells after chemotherapy.54

The inhibition of antigen presentation by MHC class I molecules is an effective strategy for tumors to escape from immune system control. Impairment of transporter associated with antigen processing (TAP) and lack of MHC class I molecules have frequently been observed in various different human cancers.66-69 In AML, CD40 and CD80 molecules are deficient, but HLA molecules and CD86 are preserved on AML blasts, and therefore constitute a prerequisite for AML blast recognition by the immune system.7 Nevertheless, further studies need to be performed to obtain deeper insights into immune escape mechanisms in AML.

**T-cell recruitment in AML**

Microenvironment and leukemia cell/T-cell interactions also play important roles in the immune escape of leukemia cells. Leukemic cells from patients with chronic lymphocytic leukemia (CLL) express high levels of immunomodulatory factors including transforming growth factor-β and interleukin-10, which suppress a T-cell response to antigens, as well as T-cell activation and expansion.70,71 Ohm et al. described tumor-induced immune suppression by overexpression of vascular endothelial growth factor (VEGF).72 Moreover, FasL has been detected on a number of tumors, including CLL and AML. FasL-positive tumor cells can induce apoptosis of T lymphocytes in vitro,73,74 thus reducing anti-leukemic immune effects. The local recruitment of anti-leukemic T cells to the AML microcompartment is also essential for the control of leukemia. The release of soluble mediators by microvascular endothelial cells supports leukemic cell proliferation and inhibition of apoptosis.75 In addition, tumor cells76 or AML blasts77 also release chemotactic chemokines such as CXCL10 or CCL5, inhibiting the migration of T cells in the bone marrow to control the proliferation of AML blasts. All of these mechanisms might impair the efficacy of tumor cell control by T lymphocytes and might, therefore, be relevant for the clinical outcome of AML patients.

**Future perspectives – how to overcome limitations of immunotherapy in AML**

The ideal time point of vaccination must be determined: given that circulating T cells detected early after chemotherapy are functional in patients with leukemia,77 immunotherapy may be started early after or even during chemotherapeutic regimes to stimulate residual memory T cells recognizing the malignant cells of the patient. The **antigen format** of the vaccine (epitope peptides, AML-derived dendritic cells,77,78 pulsed or transfected dendritic cells,79 whole cell vaccines, donor lymphocyte infusion77,80 or LAA-stimulated donor lymphocyte infusion) inducing a strong but tumor-specific immune response in AML patients **in vitro** and **in vivo** needs to be optimized. Appropriate **adjuvants** might play a key role in breaking the immune tolerance in AML patients; examples are synthetic oligonucleotides comprising a certain DNA motif (CpG motif),81 effective cytokines such as interleukin-12,82,83 granulocyte-monocyte colony-stimulating factor or/and Freund’s incomplete adjuvant (montanide).84 Possible strategies to overcome T-cell defects induced by special factors of the AML microenvironment include inhibition of VEGF or CXCL1085,86 or targeting FasL.87 So far, CD4+ T-cell epitopes have been characterized for only some of the LAA described in this review, e.g. WT1,88 and further epitopes need to be identified, because CD4+ T-cell activation is a **sine qua non** for the generation of sufficiently high titers of LAA-directed antibodies (surface LAA) and/or high frequencies of CD8+ T cells (intracellular LAA).

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