Heat Shock Proteins in Lymphoma Immunotherapy

Zarema Albakova1,2*, Yana Mangasarova3 and Alexander Sapozhnikov1,2

1 Department of Biology, Lomonosov Moscow State University, Moscow, Russia, 2 Department of Immunology, Shemyakin and Ovchinnikov Institute of Bioorganic Chemistry RAS, Moscow, Russia, 3 National Research Center for Hematology, Moscow, Russia

Immunotherapy harnessing the host immune system for tumor destruction revolutionized oncology research and advanced treatment strategies for lymphoma patients. Lymphoma is a heterogeneous group of cancer, where the central roles in pathogenesis play immune evasion and dysregulation of multiple signaling pathways. Immunotherapy-based approaches such as engineered T cells (CAR T), immune checkpoint modulators and NK cell-based therapies are now in the frontline of lymphoma research. Even though emerging immunotherapies showed promising results in treating lymphoma patients, low efficacy and on-target/off-tumor toxicity are of a major concern. To address that issue it is suggested to look into the emerging role of heat shock proteins. Heat shock proteins (HSPs) showed to be highly expressed in lymphoma cells. HSPs are known for their abilities to modulate immune responses and inhibit apoptosis, which made their successful entry into cancer clinical trials. Here, we explore the role of HSPs in Hodgkin and Non-Hodgkin lymphoma and their involvement in CAR T therapy, checkpoint blockade and NK cell-based therapies. Understanding the role of HSPs in lymphoma pathogenesis and the ways how HSPs may enhance anti-tumor responses, may help in the development of more effective, specific and safe immunotherapy.

Keywords: heat shock proteins, lymphoma, CAR T, CAR NK, checkpoint inhibitors

INTRODUCTION

Lymphoma is a heterogeneous cancer divided into two major types such as Hodgkin lymphoma (HL) and Non-Hodgkin lymphoma (NHL) (1, 2). In oncology research, management of lymphoma stands out as the choice of treatment is largely based on the results obtained from prospective clinical trials (1). Standard treatment regimen includes chemotherapy and radiation therapy for the treatment of HL and chemotherapy combined with anti-CD20 antibodies for NHL patients, reaching the cure rate of 80-90% (1, 2). Even though the response rate is high, treatment-related toxicity such as induction of second malignancy and cardiotoxicity is of a major concern (1). Following initial treatment, 10-30% of lymphoma patients develop refractory or recurrent (r/r) disease which is treated with high-dose chemotherapy followed by an autologous hematopoietic stem cell transplantation (ASCT) (1, 2). The overall goal of current and emerging treatments for HL and NHL is to cure disease and minimize treatment-related toxicity (1, 2). Current treatments for lymphoma patients are summarized in Table 1. Recently approved treatments for r/r HL and NHL subtypes include anti-CD30 antibody-drug conjugate brentuximab vedotin, PD1 inhibitors...
Heat shock proteins (HSPs) are molecular chaperones highly expressed in various types of cancer. HSPs are classified into several families such as HSP110, HSP90, HSP70, HSP40, chaperonins and HSPB (30). HSPs are largely known for their role in blocking apoptosis which was further translated into development of HSP inhibitors (31–49). Along this line, Kamal and colleagues showed that HSP90 inhibitor 17-allylamino-17-demethoxy-geldanamycin (17-AAG) selectively targets cancer cells (50). In light of the reported, several HSP90 inhibitors such as alvespimycin (NCT01126502), luminespib (NCT01485536), PU-H71 (NCT01581541) and SNX-5422 (NCT02914327) currently are assessed in clinical trials for the treatment of lymphoma patients. Furthermore, HSPs showed to be potent immune system activators through the induction of cytotoxic lymphoma patients. Furthermore, HSPs IN HODGKIN LYMPHOMA

Hodgkin lymphoma (HL) is a B cell lymphoma divided into classic HL (cHL) which accounts for the majority of the cases and nodular lymphocyte-predominant HL (NLPHL) (1). Histologically, cHL is classified into four types such as nodular sclerosis HL (NSHL), mixed cellularity HL (MCHL), lymphocyte-rich HL (LRHL) and lymphocyte-depleted HL (LDHL) (1).

HSP90, HSP70, HSP40, chaperonins and HSPB (30). HSPs are largely known for their role in blocking apoptosis which was further translated into development of HSP inhibitors (31–49). Along this line, Kamal and colleagues showed that HSP90 inhibitor 17-allylamino-17-demethoxy-geldanamycin (17-AAG) selectively targets cancer cells (50). In light of the reported, several HSP90 inhibitors such as alvespimycin (NCT01126502), luminespib (NCT01485536), PU-H71 (NCT01581541) and SNX-5422 (NCT02914327) currently are assessed in clinical trials for the treatment of lymphoma patients. Furthermore, HSPs showed to be potent immune system activators through the induction of cytotoxic lymphoma patients. Furthermore, HSPs IN HODGKIN LYMPHOMA

Hodgkin lymphoma (HL) is a B cell lymphoma divided into classic HL (cHL) which accounts for the majority of the cases and nodular lymphocyte-predominant HL (NLPHL) (1). Histologically, cHL is classified into four types such as nodular sclerosis HL (NSHL), mixed cellularity HL (MCHL), lymphocyte-rich HL (LRHL) and lymphocyte-depleted HL (LDHL) (1).

HSP90, HSP70, HSP40, chaperonins and HSPB (30). HSPs are largely known for their role in blocking apoptosis which was further translated into development of HSP inhibitors (31–49). Along this line, Kamal and colleagues showed that HSP90 inhibitor 17-allylamino-17-demethoxy-geldanamycin (17-AAG) selectively targets cancer cells (50). In light of the reported, several HSP90 inhibitors such as alvespimycin (NCT01126502), luminespib (NCT01485536), PU-H71 (NCT01581541) and SNX-5422 (NCT02914327) currently are assessed in clinical trials for the treatment of lymphoma patients. Furthermore, HSPs showed to be potent immune system activators through the induction of cytotoxic lymphoma patients. Furthermore, HSPs IN HODGKIN LYMPHOMA

Hodgkin lymphoma (HL) is a B cell lymphoma divided into classic HL (cHL) which accounts for the majority of the cases and nodular lymphocyte-predominant HL (NLPHL) (1). Histologically, cHL is classified into four types such as nodular sclerosis HL (NSHL), mixed cellularity HL (MCHL), lymphocyte-rich HL (LRHL) and lymphocyte-depleted HL (LDHL) (1).

HSP90, HSP70, HSP40, chaperonins and HSPB (30). HSPs are largely known for their role in blocking apoptosis which was further translated into development of HSP inhibitors (31–49). Along this line, Kamal and colleagues showed that HSP90 inhibitor 17-allylamino-17-demethoxy-geldanamycin (17-AAG) selectively targets cancer cells (50). In light of the reported, several HSP90 inhibitors such as alvespimycin (NCT01126502), luminespib (NCT01485536), PU-H71 (NCT01581541) and SNX-5422 (NCT02914327) currently are assessed in clinical trials for the treatment of lymphoma patients. Furthermore, HSPs showed to be potent immune system activators through the induction of cytotoxic lymphoma patients. Furthermore, HSPs IN HODGKIN LYMPHOMA

Hodgkin lymphoma (HL) is a B cell lymphoma divided into classic HL (cHL) which accounts for the majority of the cases and nodular lymphocyte-predominant HL (NLPHL) (1). Histologically, cHL is classified into four types such as nodular sclerosis HL (NSHL), mixed cellularity HL (MCHL), lymphocyte-rich HL (LRHL) and lymphocyte-depleted HL (LDHL) (1).
TRKB showed to be aberrantly expressed in HRS cells of HL patients, while no expression of these RTKs was observed in normal B cells or B-cell NHL cells (87). Furthermore, aberrant expression of mitogen-activated protein kinase (MAPK)/ERK has been reported in HL (88). In light of the reported, HSP90 inhibitor 17-AAG showed to deplete AKT and inhibit extracellular signal-regulated kinase (ERK) phosphorylation, leading to growth arrest and apoptosis in HL cell lines (89) (88). This was further supported by the finding that HSP90 inhibitor celastrol induced anti-tumor effects in HRS cells by downregulating RAS, ERK1/2 and c-Fos (90). In another experiment, inhibition of HSP90 by geldanamycin induced apoptosis in HRS cells with wild-type IKBα in p53-independent manner (91). Taken together, these observations suggest that targeting AKT, NF-kB and MAPK/ERK pathways with HSP90 inhibitors may prove effective in HL treatment.

In addition to unique immunophenotype and multiple deregulated signaling pathways, HRS cells express high level of HSPs. Hsu and colleagues assessed HSP expression of formalin-fixed, paraffin-embedded tissues derived from patients with different cHL subtypes (80). High cytoplasmic expression of HSP90 and HSP60 in HRS cells was found in NSHL, MCHL, LRHL and LDHL (80). By contrast, no cytosolic HSP27 expression was found in HRS cells in LRHL and low expression in LDHL while 20% of patients with NSHL and MCHL showed strong HSP27 expression (80). Later, Santon and co-workers used tissue microarray to analyze immunohistochemical expression of HSPs in HRS cells of cHL patients (79). More than 90 percent of cHL patients in HRS cells showed high cytoplasmic expression of HSP60, HSP10, HSP90, and CDC37, nuclear HSF1 whereas HSP110 showed to be highly expressed in nucleus and cytoplasm of HRS cells (79). Positive cytoplasmic staining of HSP70 and cytoplasmic/nuclear expression of HSP40 was observed in 78% of cHL patients whereas 54% had positive cytoplasmic expression of HSP27 (79). Expression of HSP90 and HSP70 positively correlated with expression of their co-chaperones CDC37 and HSP40, respectively (79). Furthermore, expression of HSP40 positively correlated with p53, caspase 9 and cellular FLICE-inhibitory protein (c-FLIP) whereas HSP70 expression correlated with caspase 3 (79). In another study, high cytoplasmic expression of HSP60 was observed in HRS cells in 100% of NSHL and MCHL cases (92).

**HSPs IN NON-HODGKIN LYMPHOMA**

Non-Hodgkin lymphoma (NHL) is comprised of B-cell lymphoma, accounting for the majority of the NHL lymphoma subtypes, while other NHLs include T-cell lymphoma and NK-cell lymphoma (93). NHL is classified into indolent (slow-growing) and aggressive (fast-growing) lymphoma. The most common indolent lymphoma is follicular lymphoma (FL), while other slow-growing lymphoma subtypes include marginal zone lymphoma (MZL), chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) and lymphoplasmacytic lymphoma (94). The most common aggressive NHL subtype is represented by diffuse large B-cell lymphoma (DLBCL), while
other aggressive lymphoma subtypes include mantle cell lymphoma (MCL), Burkitt lymphoma (BL) and primary effusion lymphoma (94).

Lymphoma cells largely depend on microenvironment for their growth and survival (95). Continuous signaling from B cell receptor (BCR), immune and stromal cells are required to support proliferation activity and survival of lymphoma cells. BCR is required for B cell survival and the loss of BCR results in impaired proliferation activity and survival of lymphoma cells. Furthermore, BCR signaling, including mutation in CD79B and CARD11, which is required for tonic BCR signaling in B lymphoma, suggesting potential use of HSP90 as a potential target for B lymphoma treatment (103, 104). Additionally, HSP90 showed to stabilize BCR kinases such as Bruton tyrosine kinase (BTK), SYK, Lyn and Akt in chronic lymphocytic leukemia cells (105). Recent studies have added more insight into the role of HSP90 in BCR signaling in NHL subtypes. Jacobson and colleagues reported that HSP90 inhibition led to the complete loss of BTK and IKKζ and downstream loss of phosphorylated ERK1/2 in mantle cell lymphoma cell lines (106). Moreover, HSP90 inhibitor showed to downregulate BTK in cells expressing BTK C481S mutation, which was found to be associated with resistance to BTK inhibitor ibrutinib in MCL and CLL patients (106–108). Importantly, Cerchietti and colleagues showed that HSP90 interacts with B-cell lymphoma-6 (Bcl-6) which was further supported by the finding that HSP90 inhibitor PU-H71 selectively killed Bcl-6-dependent DLBCL cells (109). Subsequently, Goldstein and co-workers used PU-H71 and tumor-enriched HSP90 (heHSP90) complexes derived from DLBCL cell lines to show that LYN, SYK, BTK and phospholipase C γ 2 (PLCγ2) are dependent on heHSP90 (110). Furthermore, treatment with PU-H71 showed to disrupt BCR signaling, calcium influx and NF-kB activity, resulting in cell growth inhibition (110). Additionally, PU-H71 in combination with ibrutinib led to the killing of lymphoma cells, suggesting that combinatorial therapeutic approach may be more effective in NHL patients (110).

In addition to continuous BCR signaling, lymphoma cells require additional signals to survive. Early experiments in establishing NHL cell lines showed that FL cells require signals from T cells for CD40-mediated interaction and IL-4 stimulation for sustained proliferation of lymphoma cells (95, 111–113). Furthermore, in NHL subtypes myeloid cells secrete high level of B cell-activating factor (BAFF) and a proliferation inducing ligand (APRIL) that are critical for survival and differentiation of B cells (73, 95, 114–117). In addition to the signals provided by immune cells, the cross-talk between stromal cells and FL cells plays important role for the growth of FL B cells [reviewed in (118)].

Members of HSP family showed to be highly expressed in NHL subtypes. Valbuena and colleagues reported moderate-to-strong cytoplasmic expression of HSP90 in 100% of cases of BL, 61% of FL patients, 59% of DLBCL, 38% of nodal MZL and 33% of cases with SLL/CLL and 30% of lymphoplasmacytic lymphoma (119). Weak cytoplasmic expression of HSP90 was observed in 43% of cases with extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (119). Patients with T-cell lymphoma showed moderate/strong cytoplasmic expression of HSP90 (119). HSP60 also showed to be highly expressed in DLBCL and high-grade FL whereas no HSP60 was detected in low-grade FL (92). NK/T-cell lymphomas showed positive cytoplasmic expression of HSP60 (92).

Recent studies have emphasized the role of HSP110 in aggressive subtypes of B-cell NHLs such as DLBCL and BL (120). Zappasodi and colleagues demonstrated that inactivation of HSP105/HSPH1 leads to downregulation of c-Myc and Bcl-6 (120). Mechanistically, HSP105 showed to interact with c-Myc and Bcl-6 in nucleus in primary human DLBCL and BL cells, suggesting that HSP105 may function as a chaperone for both c-Myc and Bcl-6 (120). Additionally, higher expression of HSP105 was found in DLBCL expressing c-Myc compared to c-Myc low/negative counterparts (120). In light of the reported, Boudesco and co-workers showed that overexpression of HSP110 resulted in upregulation of NF-kB, whereas silencing of HSP110 downregulated NF-kB, suggesting that there is an interplay between HSP110 and NF-kB (121). Mechanistically, HSP110 showed to stabilize myeloid differentiation factor 88 (MyD88), leading to chronic NF-kB activation in ABC-DLBCL (121). Therefore, targeting HSP110 may be a promising strategy for the treatment of B-cell NHLs.

Phase II clinical trial was conducted to assess the safety and efficacy of HSP90 inhibitor AUY922 in patients with r/r DLBCL and peripheral T-cell lymphoma (PTCL) (92). Overall, 14 patients with DLBCL and 6 with PTCL were enrolled, 1 patient with DLBCL reached complete response (CR) and 1 patient with PTCL achieved partial response (122). Treatment-related adverse effects included fatigue, visual disturbance that was fully reversible and anemia (122). Authors concluded that HSP90 inhibitors may be a good target in some cases, though, combination with chemotherapeutic agents and histone deacetylase (HDAC) inhibitors may be used to improve anti-tumor activity (122). Several studies assessing combination of HSP90 inhibitors with chemotherapeutic drugs such as fludarabine, doxorubicin, cytarabine, melphalan, or HDAC inhibitors demonstrated promising results in hematological malignancies (122–126). Taken together, NHL subtypes have high expression of specific HSP members, however, use of combinatorial approach in NHL patients warrants further investigation.

**HSPs AND EMERGING LYMPHOMA IMMUNOTHERAPY**

**HSPs and CAR T**

CAR T therapy involves *in vivo* expansion and genetic modification of an autologous (self) or allogeneic (donor) T
cells that specifically identify and eliminate cognate target ligand (127, 128). CAR consists of antigen-recognition domain represented by a single-chain variable fragment (scFv), hinge, transmembrane and intracellular signaling domains (127). Majority of CARs contain CD3ζ which is critical for T cell receptor (TCR) signaling (129). Due to low CAR T cell activity and persistence, second generation CARs have been developed that integrated co-stimulatory domains derived from CD28 or 4-1BB into the CAR design (128, 129). Importantly, CAR T cells that contain CD28 domains differentiate into effector memory T cells whereas 4-1BB-domain CAR T cells differentiate into central memory T cells (128, 130).

CAR T showed to be effective in the treatment of B-cell malignancies (129). In 2017 the first CAR T immunotherapy tisagenlecleucel (CD19-specific 4-1BB-CAR) was approved by FDA for the treatment of r/r B-cell acute lymphoblastic leukemia (B-ALL) (128). Later, in 2018, axicabtagene ciloucel (CD19-specific CD28-CAR) was approved for the treatment of r/r DLBCL (93). Nevertheless, the main challenge in CAR T therapy now is to find an antigen universally expressed on tumor cells that can be targeted by CAR T. Since HRS cells almost exclusively express CD30, CD30 was proposed as an attractive target for the CAR T therapy. Up till now only 3 studies assessed the efficacy and safety of CD30 CAR T immunotherapy for the treatment of Hodgkin lymphoma (129). Recently, Ramos and colleagues have conducted two phase I/II clinical trials where autologous CD30 CAR TTs were administered to patients with r/r Hodgkin lymphoma after lymphodepletion with fludarabine in combination with either bendamustine or cyclophosphamide (131). The overall response rate (ORR) for 32 patients was 72%, 19 (59%) of which achieved a complete remission (131). It is encouraging that no neurotoxicity was observed. Cytokine release syndrome (CRS) and skin rash that occurred in 10 and 20 patients, respectively, were found to be associated with cyclophosphamide rather than with bendamustine and both spontaneously resolved (131). In another study, Wang and colleagues designed anti-CD30 CAR and conducted a pilot study in patients with r/r Hodgkin lymphoma (132). After lymphodepletion, patients were infused with anti-CD30 CAR Ts. A total of 9 patients received CD30 CAR T infusion, 3 achieved CR, six experienced CRS from which 4 were low-grade and no neurotoxicity was observed (132). Authors also demonstrated promising results in combination therapy where CD30 CAR T treatment was combined with anti-PD-1 antibody (132). Notably, Watanabe and colleagues showed that CD30 induces expression of HSP90α and HSP90β in chL by activating heat shock factor 1 (HSF1) (133). Since CD30 and HSP90 are overexpressed in cHL, future studies should explore the effect of anti-CD30 CAR T therapy on HSP90 (133).

The use of CARs against HSP70 was proposed by Smith and colleagues (134). Their invention particularly aims to target membrane-bound form of HSP70, so that specifically HSP70-surface positive tumor cells can be killed (134). Similar to the Smith group, Claffey and co-workers identified heavy chain antibody (HCAb2) that selectively targets HSP90 on malignant cells (135). Based on their findings, authors described an antibody that specifically binds to the cell surface HSP90β isofrom (135, 136). Therefore, targeting surface expression of HSPs can be a new promising strategy for the development of more efficient CAR T therapy (Figure 2).

Due to on-target/off-tumor toxicity that associated with the use of CAR T therapy, several investigators proposed that the activity of CAR T cells can be controlled by thermal regulation with the use of HSP-based promoters (pHSP) (141, 142). Shapiro and colleagues used genetically engineered circuits pHSP-CAR to induce CAR expression in T cells in response to thermal stimuli (142). Studies assessing the use of pHSP for thermal control of CAR T highlighted that, despite their names, HSP members respond to various cellular stresses such as heat, hypoxia, radiation, heavy metal toxicity and cytokines (142–144). Therefore, the choice of HSP-based promoter should largely depend on the context in which these promoters will be used (142).

Several investigators demonstrated that HSP90 is crucial for the functional activity of T lymphocytes. For example, Bae and coworkers demonstrated that HSP90 inhibition downregulates the expression of CD3, CD4, CD8 as well as CD28, CD40L and αβ receptors and cripples T cell proliferation and interferon-γ (IFN-γ) secretion (145). In another study, pharmacological blocking of HSP90 resulted in decreased expression of Linker

![Diagram](Image)
TABLE 1 | Current treatments for HL and NHL.

| Lymphoma type | Standard treatment regimen | Refs |
|---------------|---------------------------|------|
| cHL           | Chemotherapy + ISRT       | (1, 3, 4) |
| r/r cHL       | High-dose chemotherapy + ASCT | (1, 4–7) |
| NLPHL         | Rituximab                 | (3, 8) |
| New agents    |                           |      |
| cHL, including r/r cHL | Brentuximab vedotin   | (1, 3, 9) |
|               | Nivolumab                 | (3, 10) |
|               | Pembrolizumab             | (3, 11) |
| Non-Hodgkin lymphoma | Standard treatment regimen |         |
| NHL, including r/r NHL | Rituximab+chemotherapy  | (2)   |
|               | Lenalidomide+Rituximab    | (2)   |
|               | High-dose chemotherapy + ASCT | (2) |
| New agents    |                           |      |
| PTCL          | Brentuximab vedotin       | (12)  |
| CLL/SLL       | Ibrutinib+rituximab       | (13, 14) |
| CLL/SLL; MCL  | Acalabrutinib             | (15–20) |
| FL and SLL    | Idelalisib                | (21)  |
| FL            | Copanlisib                | (22)  |
| r/r CLL/SLL   | Duvelisib                 | (23)  |
| r/r primary mediastinal BCL | Pembrolizumab       | (24, 25) |
| r/r DLBCL     | Tisagenlecleucel          | (26)  |
| r/r DLBCL     | Axicabtagene clicoucle    | (27, 28) |

ISRT, Involved site radiation therapy; ASCT, autologous haematopoietic stem cell transplantation; cHL, classic Hodgkin lymphoma; NLPHL, nodular lymphocyte-predominant Hodgkin lymphoma; r/r, Refractory or recurrent disease; PTCL, peripheral T-cell lymphoma; CLL, chronic lymphocytic leukemia (CLL); SLL, small lymphocytic lymphoma; MCL, mantle cell lymphoma.

for activation of T cells (LAT) in activated T cells (146). Therefore, taking into account that HSP90 is important for the T cell function and phenotype, and that CAR T-containing CD28 and CD3 domains may affect intracellular and extracellular HSP90 expression, further studies should address the effect of CAR T on HSP90 expression.

HSPs and NK Cell-Based Immunotherapy

The immunosuppressive TME specifically inhibits functional activity and proliferation of NK cells (76). Several investigators reported deficiency in the number of NK cells in the biopsies of cHL patients (76, 147). Moreover, lower number of circulating NK cells were detected in peripheral blood of cHL patients (76, 148, 149). The main goal of NK-based immunotherapy in HL is to reactivate NK cells (150). Boll and colleagues demonstrated that HSP90 inhibitor called BIIB021 combined with doxorubicin and gencitabine selectively killed Hodgkin lymphoma cells by inhibiting NF-kB activation (150). Moreover, HSP90 inhibition resulted in upregulation of NKG2D ligands such as MHC class I chain-related A (MICA), MICB and ULBP2 on HL cells, making HL cells susceptible to NK-mediated killing (150). In line with that, Fionda and colleagues demonstrated that HSP90 inhibition upregulates MICA and MICB and leads to increased NK cell degranulation in myeloma cell lines (151).

Contrary to T cells, NK cells do not recognize an antigen in the form of MHC-peptide complex, but rather sense the absence of self-MHC class I on tumor cells. HSP90 and HSP70 chaperones showed to be crucial for antigen presentation by MHC I molecule. Binder and colleagues reported that peptide antigens bound to HSPs, such as HSP90, HSP70, gp96, were presented 100 fold more efficiently by MHC I compared to free peptides (152, 153). Callahan and co-workers demonstrated that HSP90 inhibition disrupts the loading of peptides on MHC I (153). Furthermore, Kunizawa and Shastri showed that TCR-1 ring complex (TRIC/CCT) chaperonin is required for the expression of peptide-loaded MHC I on the cell surface (154). Later the same team found that inhibition of HSP90a or co-chaperone carboxyl terminus of Hsc70-interacting protein (CHIP) reduced presentation of peptide-bound MHC I on the cell surface (155).

Several investigators proposed the use of engineered NK cells as promising strategy for adoptive cell therapy in hematological malignancies (156). NK cells that are used in adoptive transfer can be allogeneic, autologous or immortalized such as NK-92 (156, 157). For research studies, NK cells can be isolated from peripheral blood or differentiated from stem cells, ex vivo expanded, activated with cytokines (IL-2, IL-15) and co-cultured with γ-irradiated feeder cells. It is important to point out that NK cells derived from peripheral blood mononuclear cells (PBMC) differ from NK cells differentiated from stem cells (156). For example, NK cells derived from cord blood showed no expression of CD57, high expression of NKG2A, lower expression of killer-immunoglobulin-like receptors (KIRs) and lower secretion of interferon-γ (156, 158). Several studies showed that NK cells can also be activated by HSP70 protein or 14-mer HSP70-derived peptide (TKD) in combination with IL-2 or IL-15 (Figure 2) (137–139). Multhoff and colleagues demonstrated that aggressive tumors have high expression of membrane-bound HSP70 (mHSP70) and that radio and/or- chemotherapy further increases surface expression of HSP70 (159–161). Furthermore, they reported that NK cells pre-activated with TKD and IL-2 recognize mHSP70 on tumor cells (137). Translating this to clinical trial, Multhoff et al. showed that four cycles of adoptive transfer of autologous NK cells pre-stimulated with TKD and IL-2 was well-tolerated and resulted in increase in the number of NK cells in peripheral blood of patients with mHSP70-positive non-small cell lung cancer (NSCLC) following radiochemotherapy in phase II clinical trial (140). Earlier, same research team demonstrated that NK cells activated with IL-2 and TKD and combined with anti-PD-1 antibody increased cytolytic activity of NK cells toward cancer cells and delayed tumor growth in vivo (162).

NK cells that express tumor-specific CARs showed to be efficiently applied in B cell malignancies (156). Currently, six CAR-NK therapies (CD19-CAR NK, CD22-CAR NK, CD19/CD22, CD7-CAR NK,CD19-t-haNK) are assessed in clinical trials for the treatment of lymphoma patients (156). Liu and colleagues used NK cells from the cord blood (CB) for incorporation of genes for CAR-CD19, IL-15 and caspase 9 as safety switch (iC9/CAR.19/IL15) to efficiently kill CD19-positive leukemia/lymphoma cells lines (156, 163). Same research group further assessed administration of HLA-mismatched iC9/CAR.19/IL15-transduced CB-NK cells in Phase I/II clinical trial to patients with r/r CD19- positive...
derived from patients with various NHL subtypes (DLBCL, B-CLL, MCL, FL, MZL, pre-B ALL) and high CD47 expression correlated with poor clinical prognosis in NHL patients (173, 175). Blocking of CD47/SIRPα with anti-CD47 monoclonal antibody resulted in phagocytosis of acute myeloid leukemia cells (173). Combination of anti-CD47 monoclonal antibody (Hu5F9-G4) and rituximab showed promising results in patients with r/r DLBCL and FL in phase I clinical trial (176). Interestingly, Cook et al. demonstrated that inhibition of glucose-regulated protein-78 (GRP78), a member of HSP70 family, downregulated CD47 expression in tumor cells, leading to enhanced macrophage infiltration (177). Moreover, co-expression of CD47 and GRP78 showed to associate with poor survival in breast cancer patients (177). HSP90 also showed to play a role in CD47 regulation as inactivation of Myc, a client protein of HSP90, resulted in reduced expression of CD47 and PD-L1 (178, 179). It is interesting to note that HSP90 inhibitor PU-H71 induced apoptosis and inhibited tumor growth in patient-derived xenograft model of MCL via downregulating Myc (179, 180). Therefore, further studies are required to understand the HSP90-MYC-CD47/PD-L1 relationship and the role of GRP78 in CD47 regulation for the development of more specific and effective CD47-based therapies.

**DISCUSSION**

Lymphoma represents a unique group of cancer derived from major effector cells of an immune system such as B cells, T and NK cells (81, 93). Immunotherapy-based approaches showed encouraging results for patients with HL and NHL, however, severe toxicity and low efficacy profiles restrict the use of immunotherapy in lymphoma patients (2, 81). To overcome these limitations, various therapeutic strategies are developed that include the use of HSPs. HSPs belong to evolutionally conserved family of chaperones that assist client proteins in folding, trafficking, degradation and showed to be involved in the most stages of cancer development (56, 181–184). High expression of HSPs on the surface correlates with the aggressiveness and resistance to therapy in many types of cancer (185, 186). Furthermore, HSPs are largely known for their critical role in regulating cell death mechanisms and immune responses (187–189).

Lymphoma cells create a complex and unique immune-modulatory tumor microenvironment, where inflammatory and stromal cells provide essential signals for growth, proliferation and survival of tumor cells (75, 95, 118). One of the major hallmark of lymphoma is represented by the deregulated critical signaling pathways including NF-kB, JAK-STAT, BCR signaling, PI3K/AKT, MAPK/ERK and apoptosis signaling pathways (82, 85–88, 190). Noticeably, specific members of HSP families, in particular, HSP90 showed to interfere with all these signaling cascades (83, 89, 103). Based on positive results from preclinical studies, several researchers proposed the use of HSP90 inhibitors for the treatment of lymphoma (122). However, result from phase II clinical trial of HSP90 inhibitor revealed low efficacy, but durable response, and
For effective development of HSP-based therapy in lymphoma, it is critical to bear in mind that different HSP members reside in different cellular compartments where they perform specific functions (30, 191, 192). For example, mitochondrial HSP90 homolog known as tumor necrosis factor receptor-associated protein 1 (TRAP1) is involved in mitochondrial bioenergetics while endoplasmic reticulum (ER) HSP90 member referred to as glucose-regulated protein 94 (GRP94/gp96/Endoplasm/HSP90B1) is critical for the unfolded protein response (193–196). It also appears that cell has some form of a balance of HSP distribution across compartments and cancer seems to impair this equilibrium, leading to the translocation of HSPs, which further reflects their functions (197–199). For example, surface expression of GRP94 showed to increase tumor immunogenicity and stabilize plasma membrane HER2 in breast cancer cells (200–202). So whether HSP-based immunotherapy also affects distribution of HSPs in HL and NHL, shifting HSPs from their primary locations is not yet clear and requires further investigation.

It is also important to point out that HSPs in extracellular milieu exist in several forms either secreted or membrane-bound and each form has distinct function (203–208). For example, dying tumor cells secrete HSP70s that serve as damage-associated molecular patters (DAMPs) and showed to elicit strong T cell response which with long-term exposure leads to the induction of immune tolerance and tumor growth (209–212). Conversely, viable tumor cells export HSP70 in exosomes which showed to activate myeloid-derived suppressor cells (MDSCs) and macrophages for the production of IL-6 and TNF-α, respectively (213, 214). Additionally, HSP70 on the surface of tumor cells serves as a recognition structure for NK cells (199, 215). In light of the reported, extracellular HSP70 activates T regulatory cells leading to the downregulation of interferon-γ and TNF-α section and upregulation of IL-10 and transforming growth factor-β (TGF-β) production (216). Along this line, interaction of extracellular HSP70 with antigen-presenting cells resulted in activation of NF-kB, leading to the production of TNF-α, IL-1β, IL-6 and IL-12 (56, 217–220). Figueiredo and colleagues reported that soluble HSP70 alone or in combination with IL-2 resulted in increased production of IFN-γ by T cells (221). Furthermore, stimulation of T cells with HSP70 and IL-2 or IL-7/IL-12/IL-15 resulted in upregulation of Granzyme B in CD4+ T cells in target-independent manner, suggesting that extracellular HSP70 can induce target-independent cytotoxicity in T- helper cells (221). In light of the reported, extracellular HSP110 induce pro-inflammatory phenotype in macrophages (222). Along this line, HSP27-positive tumor-derived exosomes enhance immunosuppressive activity of MDSCs whereas soluble HSP27 induces tolerogenic phenotype in macrophages (223, 224). Furthermore, extracellular HSP27 inhibits differentiation of monocytes to DCs (225). Therefore, taking into account immunologic role of extracellular HSPs, it is important to study their functions in lymphoma pathogenesis and further monitor expression of HSPs in different stages and subtypes of HL and NHL.

Despite their extracellular roles in tumor immunology, HSP members have also distinct intracellular immunologic functions. For example, ER HSP90 homolog GRP94 plays important role in immunosuppressive activity of T regulatory cells, in lymphopoiesis of T and B cells, in production of proinflammatory cytokines by tumor-associated macrophages, in the regulation of platelet GPIbα subunit of GPIb-IX-V complex and maturation of dendritic cells (195, 201, 202, 226–231). Along this line, mitochondrial HSP70 homolog GRP75/mtHSP70/mortalin/HSPA9 showed to interact with complement C9 and protect tumor cell from complement-dependent cytotoxicity (232–234). Furthermore, HSPs regulate an important component of innate immune response- the Nod-like receptor protein-3 (NLRP3) inflammasome (235, 236). Therefore, taking into account that central role in lymphoma pathogenesis play immune evasion mechanisms, intracellular immunologic roles of HSPs should also be considered for the development of more effective and safe HSP-based immunotherapy for the HL and NHL treatment.

HSP chaperones also showed to interact with each other. For example, mortalin interacts with HSP60 and HSP90 whereas GRP94 interacts with binding immunoglobulin protein (Bip/GRP78/HSPA5) (234, 237–239). Furthermore, individual homologs may have specific client networks. For example, ER HSP90 member GRP94 has client network that does not overlap with client network of cytosolic HSP90 homologs (195, 240, 241). Conversely, members from different HSP families may have overlapping client network. For example, HSP110 and HSP90 showed to stabilize c-Myc and Bcl-6 (109, 120, 179). Therefore, it is critical to note that blocking HSP member may further affect its co-chaperones, its client network and other HSP chaperones. Therefore, further studies should explore what happens on the level of individual HSP members in different subtypes of HL and NHL lymphoma and whether specific blocking of a particular homolog and, hence, its client and co-chaperone network, will be more advantageous for the lymphoma treatment.

HSP90 showed to affect CD3 and CD28, thus, the effect of HSP90 on CAR- containing CD3 and CD28-derived domains requires further investigation (133). From the other hand, HSP70-derived peptide TKD has been used for ex vivo activation of NK cells for adoptive transfer therapy and, since no severe toxicity was observed for NK-based immunotherapy, this strategy may be exploited for the development of lymphoma immunotherapy (140). In light of the reported, two research teams proposed to target membrane-bound HSP70 and HSP90 isoforms on tumors by CARs (134, 136).

Evidently, HSP90 via its client network (NPM/ALK and Myc) showed to be involved in the regulation of immune checkpoints such as PD-L1 and CD47 whereas HSP70 ER member GRP78 showed to be co-expressed with CD47 (171, 177–179). Since combination of HSP90 inhibitors with either anti-PD-1, anti-PD-L1 or anti-CTLA-4 antibodies showed anti-tumor effect in mouse models, combinatorial approaches of using HSP90 inhibitors and checkpoint inhibitors or HSP70 inhibitors coupled with anti-CD47 antibodies may further improve anti-tumor response (167, 172).
Another strategy to improve therapy responses involves the use of biomarkers that can predict clinical outcome. Large body of evidence suggests that extracellular HSPs can be used as predictive, prognostic and diagnostic biomarkers of cancer (31, 63, 64, 242–244). Further studies should be performed to assess expression of HSPs in extracellular milieu in their potential to predict clinical response in patients with HL and NHL. Recently, Dunphy and colleagues have conducted phase I clinical trial to test the safety and feasibility of administering 124I-PU-H71 radiologic agent followed by positron emission tomography (PET) to detect HSP90 within epichaperome complex in various types of tumors, thus supporting further development of HSP90-based targeted-therapeutics (245).

Taken together, members of HSP family may be exploited for the development of more efficacious treatment, though, further studies are required to understand the effect of HSP expression in various lymphoma subtypes and their use in the development of T/NK-based immunotherapies and combination approaches. Moreover, the role of HSPs as biomarker to predict clinical outcome in lymphoma patients warrants further investigation.

CONCLUSION

Lymphoma is a heterogeneous group of cancer, derived from immune cells and characterized into two major subtypes such as Hodgkin and Non-Hodgkin lymphoma. HSP members in particular HSP90, HSP60 and HSP70 are highly expressed in most subtypes of HL and NHL lymphoma. Evidently, HSPs play a major role in hallmarks of lymphoma pathogenesis including their involvement in immune evasion and dysregulation of key signaling cascades. Exploiting HSPs in immunotherapy-based approaches and as biomarkers for the lymphoma therapy may prove effective, however, requires further investigation.

REFERENCES

1. Connors JM, Cozen W, Steidl C, Carbone A, Hoppe RT, Flechtner H-H, et al. Hodgkin lymphoma. Nat Rev Dis Primers (2020) 6(1):61. doi: 10.1038/s41570-020-0189-6
2. Andrew DZ, Leo IG, Jeremy SA, Ranjana HA, Nancy LB, Paolo FC, et al. NCCN Guidelines Insights: B-Cell Lymphomas, Version 3.2019. J Natl Compr Canc Netw (2019) 17(6):650–61. doi: 10.6004/jnccn.2019.0029
3. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines. Hodgkin lymphoma (2019). NCCN. Available at: https://www.nccn.org/professionals/physician_gls/default.aspx#site (Accessed 21 February 2021).
4. Eichenauer DA, Engert A, André M, Federico M, Illidge T, Hutchings M, et al. Hodgkin’s lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol (2014) 25:i170–5. doi: 10.1093/annonc/mdj181
5. Kuruvilla J, Keating A, Crump M. How I treat relapsed and refractory Hodgkin lymphoma. Blood (2011) 117(16):e208–17. doi: 10.1182/blood-2010-09-288373
6. Linch DC, Goldstone AH, McMillan A, Chopra R, Vaughan Hudson G, Winfield D, et al. Dose intensification with autologous bone-marrow transplantation in relapsed and resistant Hodgkin’s disease: results of a BNLI randomised trial. Lancet (1993) 341(8852):1051–4. doi: 10.1016/0140-6736(93)92411-L
7. Schmitz N, Pfistner B, Sextro M, Sieber M, Carella AM, Haenel M, et al. Aggressive conventional chemotherapy compared with high-dose chemotherapy with autologous haemopoietic stem-cell transplantation for relapsed chemosensitive Hodgkin’s disease: a randomised trial. Lancet (2002) 359(9323):2065–71. doi: 10.1016/S0140-6736(02)08938-9
8. Advani RH, Hoppe RT. How I treat nodular lymphocyte predominant Hodgkin lymphoma. Blood (2013) 122(26):4182–8. doi: 10.1182/blood-2013-07-453241
9. U.S. Food and Drug Administration. FDA expands approval of Adcetris for first-line treatment of Stage III or IV classical Hodgkin lymphoma in combination with chemotherapy (2018). Available at: https://www.fda.gov/news-events/press-announcements/fda-expands-approval-adcetris-first-line-treatment-stage-iii-or-iv-classical-hodgkin-lymphoma (Accessed 21 February 2021).
10. U. S. Food and Drug Administration. Nivolumab (Opdivo) for Hodgkin Lymphoma (2016). Available at: https://www.fda.gov/drugs/resources-information-approved-drugs/nivolumab-opdivo-hodgkin-lymphoma (Accessed 21 Feb 2021).
11. U. S. Food and Drug Administration. FDA extends approval of pembrolizumab for classical Hodgkin lymphoma (2020). Available at: https://www.fda.gov/drugs/drug-approvals-and-databases/fda-extends-approval-pembrolizumab-classical-hodgkin-lymphoma (Accessed 21 February 2021).
12. U.S. Food and Drug Administration. FDA approves first-line treatment for peripheral T-cell lymphoma under new review pilot (2018). Available at: https://www.fda.gov/news-events/press-announcements/fda-approves-first-line-treatment-peripheral-t-cell-lymphoma-under-new-review-pilot (Accessed 21 February 2021).
13. U.S. Food and Drug Administration. FDA approves ibrutinib plus rituximab for chronic lymphocytic leukemia (2020). Available at: https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-ibrutinib-plus-rituximab-chronic-lymphocytic-leukemia (Accessed 21 February 2021).
14. Shanafelt TD, Wang XV, Kay NE, Hanson CA, O’Brien S, Barrientos J, et al. Ibrutinib–Rituximab or Chemoimmunotherapy for Chronic Lymphocytic Leukemia. New Engl J Med (2019) 381(5):432–43. doi: 10.1056/NEJMoa1817073
15. U.S. Food and Drug Administration. Project Orbis: FDA approves acalabrutinib for CLL and SLL (2019). Available at: https://www.fda.gov/drugs/resources-information-approved-drugs/project-orbis-fda-approves-acalabrutinib-cll-and-sll (Accessed 21 February 2021).
16. Sharman JP, Egyed M, Jurczak W, Skarbnik A, Pagel JM, Flinn IW, et al. Acalabrutinib with or without obinutuzumab versus chlorambucil and pembrolizumab in patients with relapsed or refractory chronic lymphocytic leukemia: a phase 3, open-label, randomised, controlled trial. Lancet (2018) 391(10120):780–91. doi: 10.1016/S0140-6736(17)31298-6

ACKNOWLEDGMENTS

The figures were created with BioRender.com.
obinutuzumab for treatment-naive chronic lymphocytic leukemia (ELEVATE-TN): a randomised, controlled, phase 3 trial. Lancet (2020) 395(10232):1278–91. doi: 10.1016/S0140-6736(20)30262-2

17. Ghia P, Plata A, Vach M, Lyvak D, Kozak T, Simkovic M, et al. ASCEND: Phase III, Randomized Trial of Acalabrutinib Versus Idelalisib Plus Rituximab or Bendamustine Plus Rituximab in Relapsed or Refractory Chronic Lymphocytic Leukemia. J Clin Oncol (2020) 38(25):2849–61. doi: 10.1200/JCO.19.03355

18. U.S. Food and Drug Administration. FDA approves pembrolizumab for acalabrutinib for mantle cell lymphoma (2017). Available at: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-acalabrutinib-mantle-cell-lymphoma (Accessed 21 February 2021).

19. Wang M, Rule S, Zinzani PL, Goy A, Casasnovas O, Smith SD, et al. Durable response with single-agent acalabrutinib in patients with relapsed or refractory mantle cell lymphoma. Leukemia (2019) 33(11):2762–6. doi: 10.1038/s41373-019-0575-9

20. Wang M, Rule S, Zinzani PL, Goy A, Casasnovas O, Smith SD, et al. Acalabrutinib in relapsed or refractory mantle cell lymphoma. (ACE-LY-004): a single-arm, multicentre, phase 2 trial. Lancet (2018) 391(10121):659–67. doi: 10.1016/S0140-6736(17)33108-2

21. Miller BW, Przeworska D, de Claro RA, Lee K, Nie L, Simpson N, et al. FDA Approval: Idelalisib Monotherapy for the Treatment of Patients with Follicular Lymphoma and Small Lymphocytic Lymphoma. Clin Cancer Res (2015) 21(7):1525. doi: 10.1158/1078-0432.CCR-14-2522

22. U.S. Food and Drug Administration. FDA grants accelerated approval to copiktra for relapsed follicular lymphoma (2017). Available at: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-copiktra-relapsed-follicular-lymphoma (Accessed 21 February 2021).

23. U.S. Food and Drug Administration. duvelisib (COPIKTRA, Verastem, Inc.) for adult patients with relapsed or refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) (2018). Available at: https://www.fda.gov/drugs/resources-information-approved-drugs/duvelisib-copiktra-verastem-inc-adult-patients-relapsed-or-refractory-pmbcl (Accessed 21 February 2021).

24. U.S. Food and Drug Administration. FDA approves pembrolizumab for treatment of relapsed or refractory PMBCL (2018). Available at: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-pembrolizumab-treatment-relapsed-or-refractory-pmbcl (Accessed 21 February 2021).

25. Zinzani PL, Thieblemont C, Melnichenko V, Bouabdallah K, Walewski J, et al. Guidelines for the nomenclature of the human heat shock proteins. Cell Stress Chaperones (2009) 14(1):105–11. doi: 10.1007/s12192-008-0068-7

26. Antonoff MB, Chugh R, Skube SJ, Dudeja V, Borja-Cacho D, Clawson KA, et al. Role of Hsp-70 in tripletide-mediated cell death of neuroblastsoma. J Surg Res (2010) 163(1):72–8. doi: 10.1016/j.jss.2010.04.047

27. Braunstein MJ, Scott SS, Scott CM, Behrman S, Walter P, Wipf P, et al. Antimyeloma Effects of the Heat Shock Protein 70 Molecular Chaperone Inhibitor MAL3-101. J Oncol (2011) 2011:232037. doi: 10.1155/2011/232037

28. Ernst K, Liebscher M, Matheja S, Granzhan A, Schmid J, Popoff MR, et al. A novel Hsp70 inhibitor prevents cell intoxication with the actin ADP-ribosylating Clostridium perfringens iota toxin. Sci Rep (2016) 6(1):20301. doi: 10.1038/srep20301

29. Hewitt SW, Smith CM, Lyon MA, Dunitrescu TP, Wipf P, Day BW, et al. Small molecule modulators of endogenous and co-chaperone-stimulated Hsp70 ATPase activity. J Bio Chem (2004) 279(49):51311–40. doi: 10.1074/jbc.M404857200

30. Howe MK, Bodoor K, Carlson DA, Hughes PF, Alwarwarah Y, Loselle DR, et al. Identification of an allosteric small-molecule inhibitor selective for the inducible form of heat shock protein 70. Chem Biol (2014) 21(12):1648–59. doi: 10.1016/j.chembiol.2014.10.016

31. Hung C-M, Su Y-H, Lin Y-H, Lin J-N, Liu L-C, Ho C-T, et al. Demethoxycurcumin Modulates Prostate Cancer Cell Proliferation via AMPK-Induced Down-regulation of HSP70 and EGFR. J Agric Food Chem (2012) 60(34):8427–34. doi: 10.1021/jf20375w

32. Hung CC, Broydos JF, Brummond KM, Chambers PG, Eyer I, Ireland AW, et al. Chemical methodology as a source of small-molecule checkpoint inhibitors and heat shock protein 70 (Hsp70) modulators. Proc Natl Acad Sci U.S.A. (2011) 108(17):6757–62. doi: 10.1073/pnas.1015251108

33. Jacobson BA, Chen EZ, Tang S, Belgum HS, McCaulley JA, Evenson KA, et al. Triptolide and its prodrug minnelide suppress Hsp70 and inhibit in vivo growth in a xenograft model of mesothelioma. Genes Cancer (2015) 6(3–4):144–52. doi: 10.18632/gncancer.55

34. Jung JH, Lee JO, Kim JH, Lee SK, You GY, Park SH, et al. Quercetin suppresses HeLa cell viability via AMPPK-induced Hsp70 and EGFR down-regulation. J Cell Physiol (2010) 223(2):408–14. doi: 10.1002/jcp.22049

35. Ko S-K, Kim J, Na Deuk C, Park S, Park S-H, Hyun J, et al. A Small Molecule Inhibitor of ATPase Activity of HSP70 Induces Apoptosis and Has Antitumor Activities. Chem Biol (2015) 22(3):391–403. doi: 10.1016/j.chembiol.2015.02.004

36. Lee JJ, Pimkina J, Frank A, Murphy ME, George DL. A small molecule inhibitor of inducible heat shock protein 70. Mol Cell (2009) 36(1):15–27. doi: 10.1016/j.molcel.2009.09.023

37. Phillips PA, Sangwan V, Borja-Cacho D, Dudeja V, Vickers SM, Saluja AK. Myricetin induces pancreatic cancer cell death via the induction of apoptosis and inhibition of the phosphatidylinositol 3-kinase (PI3K) signaling pathway. Cancer Lett (2011) 308(2):181–9. doi: 10.1016/j.canlet.2011.05.002

38. Rörole A-L, Gobbo J, De Thonel A, Schmitt E, Pais de Barros JP, Hammann A, et al. Peptides and Aptamers Targeting HSP70: A Novel Approach for Anticancer Chemotherapy. Cancer Res (2011) 71(2):484. doi: 10.1158/0008-5472.CAN-10-1443

39. Rodina A, Patel PD, Kang Y, Patel Y, Baeklini I, Wong MJ, et al. Identification of an allosteric pocket on human hsp70 reveals a mode of inhibition of this therapeutically important protein. Chem Biol (2013) 20(12):1469–80. doi: 10.1016/j.chembiol.2013.10.008

40. Rousalova I, Banerjee S, Sangwan V, Evenson K, McAuley JA, Kratzke R, et al. Minnelide: a novel therapeutic that promotes apoptosis in non-small cell lung carcinoma in vivo. PloS One (2013) 8(10):e77411. doi: 10.1371/journal.pone.0077411

41. Schmitt E, Maingret L, Puig PE, Rörole AL, Ghiringhelli F, Hammann A, et al. Heat shock protein 70 neutralization exerts potent antitumor effects in animal models of colon cancer and melanoma. Cancer Res (2006) 66(8):4191–7. doi: 10.1158/0008-5472.CAN-05-3778

42. Williams DR, Ko S-K, Park S, Lee M-R, Shin I. An Apoptosis-Inducing Small Molecule That Binds to Heat Shock Protein 70. Angewandte Chemie Int Edition (2008) 47(39):8466–9. doi: 10.1002/anie.200802801

43. Speranza G, Anderson L, Chen AP, Do K, Eugeni M, Weil M, et al. First-in-human study of the epichaperome inhibitor PU-H71: clinical results and metabolic profile. Invest New Drugs (2018) 36(2):230–9. doi: 10.1007/s10637-017-0495-3
50. Kamal A, Thao L, Sensintaffar J, Zhang L, Boehm MF, Fritz IC, et al. A high-affinity conformation of Hsp90 confers tumour selectivity on Hsp90 inhibitors. *Nature* (2003) 423(6956):407–10. doi: 10.1038/nature01913
51. Udonó H, Srivastava PK. Comparison of tumor-specific immunogenicities of stress-induced proteins gp96, hsp90, and hsp70. *J Immunol* (1994) 152 (11):5398.
52. Srivastava P. Interaction of heat shock proteins with peptides and antigen presenting cells: chaperoning of the innate and adaptive immune responses. *Annu Rev Immunol* (2002) 20:395–425. doi: 10.1146/annurev.immunol.20.100301.064801
53. Blachère NE, Li Z, Chandawarkar RY, Suto R, Jaiakira NS, Basu S, et al. Heat shock protein-peptide complexes, reconstituted in vitro, elicit peptide-specific cytotoxic T lymphocyte response and tumor immunity. *Exp Med* (1997) 186(6):1315–22. doi: 10.1084/jem.186.8.1315
54. Weng D, Calderwood SK, Gong J. Preparation of a heat-shock protein 70-based vaccine from DC-tumor fusion cells. *Methods Mol Biol* (2011) 787:255–65. doi: 10.1007/978-1-61779-295-3_19
55. Li X, Cai X, Zhang Z, Ding Y, Ma R, Huang F, et al. Memetic Heat Shock Protein Mediated Immune Process to Enhance Cancer Immunotherapy. *Nano Lett* (2020) 20(6):4454–63. doi: 10.1021/acs.nanolett.0c01230
56. Albakova Z, Armeev GA, Kanevskiy LM, Kovalenko EL, Sapozhnikov AM. HSP70 Multi-Functionality in Cancer. *Cells* (2020) 9(3). doi: 10.3390/cells903357
57. Milani V, Stangl S, Issels R, Gehrmann M, Wagner B, Hube K, et al. Heat shock protein 27 in malignant melanoma. *Clin Cancer Res* (2015) 21(18):5398–408. doi: 10.1158/1078-0432.CCR-15-0083
58. Maeda Y, Yoshimura K, Matsui H, Shindo Y, Tamesa T, Tokumitsu Y, et al. Dendritic cells transfected with heat-shock protein 70 messenger RNA for patients with hepatitis C virus-related hepatocellular carcinoma: a phase I dose escalation clinical trial. *Cancer Immunol Immunother* (2015) 64 (8):1047–56. doi: 10.1007/s00262-015-1709-1
59. Kokowski K, Stangl S, Seier S, Hildebrandt M, Vaupel P, Multhoff G. Radiochemotherapy combined with NK cell transfer followed by second-line PD-1 inhibition in a patient with NSCLC stage IIIb inducing long-term tumor control: a case study. *Strahlenther Onkol* (2019) 195(4):352–61. doi: 10.11588/0323-0432.CCR-03-0683
60. Specht HM, Ahrens N, Blankenstein C, Düell T, Fietkau R, Gaipl US, et al. Constitutive nuclear factor-kappaB-RelA activation is required for radiation therapy in patients with squamous cell carcinoma of the head and neck. *Radiat Oncol (London Engundy)* (2014) 9:131–1. doi: 10.1186/1748-717X-9-131
61. Gehrmann M, Specht HM, Bayer C, Brandstetter M, Chizzali B, Duma M, et al. Hsp70—a biomarker for tumor detection and monitoring of outcome of radiation therapy in patients with squamous cell carcinoma of the head and neck. *Radiat Oncol* (2014) 9:131–1. doi: 10.1186/1748-717X-9-131
62. Rong B, Zhao C, Liu H, Ming Z, Cai X, Gao W, et al. Erratum: Identification and verification of Hsp90-beta as a potential serum biomarker for lung cancer. *Am J Cancer Res* (2016) 6(6):1460–1460.
63. Rong B, Zhao C, Liu H, Ming Z, Cai X, Gao W, et al. Identification and verification of Hsp90-beta as a potential serum biomarker for lung cancer. *Am J Cancer Res* (2016) 4(6):874–85.
102. Davis RE, Ngo VN, Lenz G, Tolar P, Young RM, Romesser PB, et al. Chronic Compagno M, Lim WK, Grunn A, Nandula SV, Brahmachary M, Shen Q, Walter R, Pan K-T, Doebele C, Comoglio F, Tomska K, Bohnenberger H, Zheng B, Fiumara P, Li YV, Georgakis G, Snell V, Younes M, et al. MEK/Heat Shock Protein 90: Molecular Pathways of Response and Potential Mechanisms of Resistance. Int J Mol Sci (2018) 19(3):836. doi: 10.3390/ijms19030836

103. Jänz M, Stühmer T, Vassilev LT, Bargou RC. Pharmacologic activation of p53-dependent and p53-independent apoptotic pathways in Hodgkin/Reed-Sternberg cells. Leukemia (2007) 21(4):772–9. doi: 10.1038/sj.leu.2404565

104. Jin H, Yoshino T, Jin Z, Oka T, Kobayashi K, Yamasaki R, et al. Expression of CHAS-C, QinH, Kannan S, Rawal S, Watkins LS, Bäio F E, et al. Mutations in Human Diffuse Large B Cell Lymphoma. Science (2010) 323(5870):1676. doi: 10.1126/science.1153629

105. Myklebust JH, Brody J, Kohrt HE, Kolstad A, Czerwinski DK, Wälchli S, Armengol M, Santos JC, Fernández-Serrano M, Profitós-Pelejá N, Ribeiro ML, Roue G. Immune-Checkpoint Inhibitors in B-Cell Lymphoma. Cancers (Basel) (2021) 13(2):214. doi: 10.3390/cancers13020214

106. Scott DW, Gascoyne RD. The tumour microenvironment in B cell lymphomas. Nat Rev Cancer (2014) 14(8):517–34. doi: 10.1038/nrc3774

107. Lam K-P, Kühn R, Rajewsky K. In Vivo Ablation of Surface Immunoglobulin on Mature B Cells by Inducible Gene Targeting Results in Rapid Cell Death. Cell (1997) 90(6):1073–83. doi: 10.1016/S0092-8674(00)08373-6

108. Myklebust JH, Brody J, Kohrt HE, Kolstad A, Czerwinski DK, Wälchli S, et al. Distinct patterns of B-cell receptor signaling in non-Hodgkin lymphomas identified by single-cell profiling. Blood (2017) 129(6):759–70. doi: 10.1182/blood-2016-05-718494

109. Cha S-C, Qin H, Kannan S, Rawal S, Watkins LS, Baio FE, et al. Nonsterotyped lymphoma B cell receptors recognize vimentin as a shared autoantigen. J Immunol (Baltimore Md 1960) (2015) 193(9):4887–98. doi: 10.4049/jimmunol.1500179

110. Young RM, Wu T, Schmitz R, Dawood M, Xiao W, Phelan JD, et al. Survival of human lymphoma cells requires B-cell receptor engagement by self-antigens. Proc Natl Acad Sci U S A (2015) 112(44):13447–54. doi: 10.1073/pnas.1514944112

111. Compagno M, Lim WK, Grunn A, Nandula SV, Brahchamay M, Shen Q, et al. Mutations of multiple genes cause deregulation of NF-kappaB in diffuse large B-cell lymphoma. Nature (2009) 459(7247):717–21. doi: 10.1038/nature07968

112. Lenz G, Davis RE, Ngo VN, Lam L, George TC, Wright GW, et al. Oncogenic <em>c-m</em>-CARD11/<em>c-m</em>-Mutations in Human Diffuse Large B Cell Lymphoma. Science (2008) 319(5870):1676. doi: 10.1126/science.1153629

113. Davis RE, Ngo VN, Lenz G, Tolar P, Young RM, Romesser PB, et al. Chronic active B-cell-receptor signalling in diffuse large B-cell lymphoma. Nature (2010) 463(7277):88–92. doi: 10.1038/nature08638

114. Walter R, Pan K-T, Doebele C, Comoglio F, Tomoka K, Bohnenberger H, et al. HSP90 promotes Burkitt lymphoma cell survival by maintaining tonic B-cell receptor signaling. Blood (2017) 129(5):598–608. doi: 10.1182/blood-2016-06-721423

115. ten Hacken E, Burger JA. HSP90, a chaperone that can make you SYK. Blood (2017) 129(5):542–4. doi: 10.1182/blood-2016-12-753152

116. Guo A, Lu P, Lee J, Zhen C, Chiosis G, Wang YL. HSP90 stabilizes B-cell receptor kinases in a multi-client interaction: PU-H71 induces CLL apoptosis in a cytoreductive microenvironment. Oncogene (2017) 36(24):3441–9. doi: 10.1038/onc.2016.494

Albakova et al. HSPs in Lymphoma Immunotherapy

Frontiers in Immunology | www.frontiersin.org March 2021 Volume 12 Article 660085 12

Best OG, Mulligan SP. Heat shock protein-90 inhibitor, NVP-AUY922, is effective in combination with fludarabine against chronic lymphocytic
leukemia cells cultured on CD40L-stromal layer and inhibits their activated/ proliferative phenotype. Leukemia (2012) 53(11):2314–20.
doi: 10.1038/lubm.2012.69
Kaiser M, Lamotte B, Mareth M, Jensen MR, Quadri C, Garcia-Echeverria C, et al. Synergistic action of the novel HSP90 inhibitor NVP-AUY922 with histone deacetylase inhibitors, melphalan, or doxorubicin in multiple myeloma. Eur J Haematol (2010) 84(4):337–44. doi: 10.1111/j.1600-0609.2009.01403.x
Rao R, Fiskus W, Yang Y, Lee P, Joshi R, Fernandez P, et al. HDAC6 inhibition enhances 17-AAG-mediated abrogation of hsp90 chaperone function in human leukemia cells. Blood (2008) 112(18):1886–93. doi: 10.1182/blood-2008-03-143644
Chavez JC, Bachmeier C, Kharfan-Dabaja MA. CAR T-cell therapy for B-cell lymphomas: clinical trial results of available products. Ther Adv Hematol (2019) 10:2046207918841581. doi: 10.1177/2046207918841581
Rafiq S, Hackett CS, Brentjens RJ. Engineering strategies to overcome the current roadblocks in CAR T cell therapy. Nat Rev Clin Oncol (2020) 17 (3):147–67. doi: 10.1038/s41571-019-0297-y
Halim L, Maher J. CAR T-cell immunotherapy of B-cell malignancy: the story so far. Ther Adv Vaccines Immunother (2020) 8:2515135520927164. doi: 10.1177/2515135520927164
Kawalekar OU, O’Connor RS, Fraelit JA, Gurov NS, Seifert AD Jr, et al. Distinct Signaling of Correzceptors Specify Metabolic Pathways and Impacts Memory Development in CAR T Cells. Immunity (2016) 44(2):380–90. doi: 10.1016/j.immuni.2016.01.021
Ramos CA, Grover NS, Beaven AW, Lulla PD, Wu M-F, Ivanova A, et al. Anti-CD30 CAR-T Cell Therapy in Relapsed and Refractory Hodgkin Lymphoma. J Clin Oncol (2020) 38(32):3794–804. doi: 10.1200/jco.20.01342
Wang D, Zeng C, Xu B, Xu JH, Wang J, Jiang LJ, et al. Anti-CD30 chimeric antigen receptor T cell therapy for relapsed/refractory CD30+ lymphoma patients. Blood Cancer J (2020) 10(1):8. doi: 10.1038/s41408-020-0274-9
Watanabe M, Nakano K, Kadin ME, Higashihara M, Watanabe T, Horie R. Anti-CD30 CAR-T Cell Therapy in Relapsed and Refractory Hodgkin Lymphoma Cells. Am J Pathol (2017) 187(1):163–75. doi: 10.1016/j.ajpath.2016.09.007
Smith J VJ, Juillerat A, Duchateau P, Susu BJ, Rajpal A. Anti-hsp70 specific chimeric antigen receptors (CARs) for cancer immunotherapy, U.S. Patent and Trademark Office (2016), US Patent. Available at: https://patentscope.wipo.int/search/en/detail.jsf?docId=US209520457
Devarakonda CV, Kita D, Phoenix KN, Clafl ey KP. Patient-derived heavy chain antibody targets cell surface HSP90 on breast tumors. BMC Cancer (2015) 15:614–4. doi: 10.1186/s12885-015-1608-z
Clafl ey KP, Devarakonda C, Kita D. ANTIBODY AND ANTIGEN-BINDING PROTEINS—TARGETING CELL SURFACE ANTIGENS IN TUMORS AND METHODS OF USE THEREOF. U.S. Patent. and Trademark Office. (2019) Available at: https://patentscope.wipo.int/search/en/detail.jsf?docId=US279826324&docDate=201603397
Multlhoff G, Pfister K, Gehrmann M, Hantschel M, Gross C, Hafner M, et al. A 14-mer Hsp70 peptide stimulates natural killer (NK) cell activity. Cell Stress Chaperones (2001) 6(4):337–44. doi: 10.1379/1466-1268(2001)006<0337:AMHPSN>2.0.CO;2
Hromadnikova I, Li S, Kotlabova K, Dickinson AM. Influence of In Vitro IL- 2 or IL-15 Alone or in Combination with Hsp 70 Derived 14-Mer Peptide (TKD) on the Expression of NK Cell Activatory and Inhibitory Receptors on Peripheral Blood T Cells, B Cells and NKT Cells. PloS One (2016) 11(3): e0151535. doi: 10.1371/journal.pone.0151535
Stangl S, Gross C, Pockley AG, Asea AA, Multlhoff G. Influence of Hsp70 and HLA-E on the killing of leukemia blasts by cytokine/Hsp70 peptide-activated human natural killer (NK) cells. Cell Stress Chaperones (2008) 13(2):221–30. doi: 10.1007/s12192-007-0008-y
Multlhoff G, Seier S, Stangl S, Sievert W, Shevtsov M, Werner C, et al. Targeted Natural Killer Cell-Based Adaptive Immunotherapy for the Treatment of Patients with NSCLC after Radiochemotherapy: A Randomized Phase II Clinical Trial. Clin Cancer Res (2020) 26(20):5368. doi: 10.1158/1078-0432.CCR-20-1142
Gamboa L, Zamatz AH, Kwong GA. Synthetic immunity by remote control. Theranostics (2020) 10(8):3652–67. doi: 10.7150/thno.41305
Abdelli MH, Lee J, Piranier DI, Shapiro MG. Thermal Control of Engineered T-cells. ACS Synthetic Biol (2020) 9(8):1941–50. doi: 10.1021/acssynbio.0c00338
Kregel KC. Invited Review: Heat shock proteins: modifying factors in physiological stress responses and acquired thermostolerance. J Appl Physiol (2002) 92(5):1777–86. doi: 10.1152/japplphysiol.01267.2001
Morimoto RI. Regulation of the heat shock transcriptional response: cross talk between a family of heat shock factors, molecular chaperones, and negative regulators. Genes Dev (1998) 12(4):3788–96. doi: 10.1101/gad.12.24.3788
160. Multhoff G, Botzler C, Wiesnet M, Müller E, Meier T, Wilmanns W, et al. A stress-inducible 72-kDa heat-shock protein (HSP72) is expressed on the surface of human tumor cells, but not on normal cells. *Int J Cancer* (1995) 61(2):272–9. doi: 10.1002/ijc.2910610222

161. Botzler C, Schmidt J, Luz A, Jennen L, Issels R, Multhoff G. Differential Hsp70 plasma-membrane expression on primary human tumors and metastases in mice with severe combined immunodeficiency. *Int J Cancer* (1998) 77(6):942–8. doi: 10.1002/(SICI)1097-0215(19980911)77:6<942::AID-IJC2>3.0.CO;2-1

162. Shevtsov M, Pitkin E, Ischenko A, Stangl S, Khachatryan W, Galibin O, et al. A decade of immune-checkpoint inhibitors in cancer therapy. *Clin Cancer Res* 2021;27(2):12-0538.

163. Liu E, Tong Y, Dotti G, Shaim H, Savoldo B, Mukherjee M, et al. Cord blood NK cells engineered to express IL-15 and a CD19-targeted CAR show long-term persistence and potent antitumor activity. *Leukemia* (2018) 32(2):520–31. doi: 10.1038/leu.2017.226

164. Proia DA, Kaufmann GF. Targeting Heat-Shock Protein 90 (HSP90) as a Complementary Strategy to Immune Checkpoint Blockade for Cancer Therapy. *Cancer Immunol Res* (2015) 3(6):583–9. doi: 10.1158/2326-6066.CIR-15-0057.

165. Shevtsov M, Pitkin E, Ischenko A, Stangl S, Khachatryan W, Galibin O, et al. Ex vivo Hsp70-Activated NK Cells in Combination With PD-1 Inhibition Significantly Increase Overall Survival in Preclinical Models of Glioblastoma and Lung Cancer. *Front Immunol* (2019) 10:1454. doi: 10.3389/fimmu.2019.001454.

166. Haggerty TJ, Dunn IS, Rose LB, Newton EE, Pandol SF, Kurnick JT. Heat shock protein 70 and glycoprotein 96 are differentially expressed on the surface of human tumor cells, but not on normal cells. *Proc Natl Acad Sci U S A* (2012) 109(12):4947–52. doi: 10.1073/pnas.1118046109.

167. Proia DA, Kaufmann GF. Targeting Heat-Shock Protein 90 (HSP90) as a Complementary Strategy to Immune Checkpoint Blockade for Cancer Therapy. *Cancer Immunol Res* (2015) 3(6):583–9. doi: 10.1158/2326-6066.CIR-15-0057.

168. Marzec M, Eletto D, Argon Y. GRP94: An HSP90-like protein specialized for protein folding and quality control in the endoplasmic reticulum. *Biochim Biophys Acta* (2012) 1823(3):774–87. doi: 10.1016/j.bbamcr.2011.10.013.

169. Marzec M, Eletto D, Argon Y. GRP94: An HSP90-like protein specialized for protein folding and quality control in the endoplasmic reticulum. *Biochim Biophys Acta* (2012) 1823(3):774–87. doi: 10.1016/j.bbamcr.2011.10.013.

170. Haggerty TJ, Dunn IS, Rose LB, Newton EE, Pandol SF, Kurnick JT. Heat shock protein 70 and glycoprotein 96 are differentially expressed on the surface of human tumor cells, but not on normal cells. *Proc Natl Acad Sci U S A* (2012) 109(12):4947–52. doi: 10.1073/pnas.1118046109.

171. Marzec M, Eletto D, Argon Y. GRP94: An HSP90-like protein specialized for protein folding and quality control in the endoplasmic reticulum. *Biochim Biophys Acta* (2012) 1823(3):774–87. doi: 10.1016/j.bbamcr.2011.10.013.

172. Marzec M, Eletto D, Argon Y. GRP94: An HSP90-like protein specialized for protein folding and quality control in the endoplasmic reticulum. *Biochim Biophys Acta* (2012) 1823(3):774–87. doi: 10.1016/j.bbamcr.2011.10.013.

173. Marzec M, Eletto D, Argon Y. GRP94: An HSP90-like protein specialized for protein folding and quality control in the endoplasmic reticulum. *Biochim Biophys Acta* (2012) 1823(3):774–87. doi: 10.1016/j.bbamcr.2011.10.013.

174. Marzec M, Eletto D, Argon Y. GRP94: An HSP90-like protein specialized for protein folding and quality control in the endoplasmic reticulum. *Biochim Biophys Acta* (2012) 1823(3):774–87. doi: 10.1016/j.bbamcr.2011.10.013.

175. Marzec M, Eletto D, Argon Y. GRP94: An HSP90-like protein specialized for protein folding and quality control in the endoplasmic reticulum. *Biochim Biophys Acta* (2012) 1823(3):774–87. doi: 10.1016/j.bbamcr.2011.10.013.

176. Marzec M, Eletto D, Argon Y. GRP94: An HSP90-like protein specialized for protein folding and quality control in the endoplasmic reticulum. *Biochim Biophys Acta* (2012) 1823(3):774–87. doi: 10.1016/j.bbamcr.2011.10.013.

177. Marzec M, Eletto D, Argon Y. GRP94: An HSP90-like protein specialized for protein folding and quality control in the endoplasmic reticulum. *Biochim Biophys Acta* (2012) 1823(3):774–87. doi: 10.1016/j.bbamcr.2011.10.013.

178. Marzec M, Eletto D, Argon Y. GRP94: An HSP90-like protein specialized for protein folding and quality control in the endoplasmic reticulum. *Biochim Biophys Acta* (2012) 1823(3):774–87. doi: 10.1016/j.bbamcr.2011.10.013.
216. Wachstein J, Bottler C, Wiesnet M, Muller E, Meier T, Willmanns W, et al. A stress-inducible 72-kDa heat-shock protein (HSP72) is expressed on the surface of human tumor cells, but not on normal cells. *Int J Cancer* (1995) 61(2):272–9. doi: 10.1002/ijc.290610222

200. Patel PD, Yang P, Seidler PM, Patel HI, Sun W, Yang C, et al. Paralog-selective Hsp90 inhibitors define tumor-specific regulation of HER2. *Nat Chem Biol* (2013) 9(11):677–84. doi: 10.1038/nchembio.1335

203. Wu BX, Hong F, Zhang Y, Ansa-Addo E, Li Z. Chapter Seven - GRP94/gp96 in Cancer: Biology, Structure, Immunology, and Drug Development. In: J Isaacs and I Whitesell, editors. *Advances in Cancer Research*, vol. 129. SAN DIEGO, USA: Elsevier Academic Press (2016). p. 165–90. doi: 10.1016/bc.2015.09.001

204. Ono K, Eguchi T, Sogawa C, Calderwood SK, Futagawa J, Kasai T, et al. HSP-200. Patel PD, Yan P, Seidler PM, Patel HJ, Sun W, Yang C, et al. Paralog-selective HSP70 stimulates cytokine production through a CD14-dependent pathway, demonstrating its dual role as a chaperone and cytokine. *Nat Med* (2000) 6(4):435–42. doi: 10.1038/4697

205. Fugieriedo C, Wittmann M, Wang D, Dressel R, Sletsman A, Blasczyk R, et al. Heat shock protein 70 (HSP70) induces cytotoxicity of T-helper cells. *Blood* (2009) 113(13):3008–16. doi: 10.1182/blood-2008-06-162727

206. Berkenhut B, Boudesco C, Collura A, Svrcek M, Richaud S, Hammann A, et al. Extracellular HSP110 skew macrophage polarization in colorectal cancer. *Oncoimmunology* (2016) 5(7):e1107264–e1107264. doi: 10.21462.OX1107264

207. Caruso Bavisotto C, Cappello F, Macario AJL, Conway de Macario E, Rajkovic D, Dojder A, C... [ et al. Immune cell stress and the organizing principle of the platelet glycoprotein Ib-IX-V complex. *Blood* (2011) 117(2):736–44. doi: 10.1182/blood-2011-01-330464

208. Gunther S, Ostheimer C, Stangl S, Specht HM, Mozes P, Jesinghaus M, et al. Increased heat shock protein (HSP70) expression on the surface of human tumor cells: role in autocrine and paracrine mechanisms. *Sci Rep* (2019) 9(1):15108. doi: 10.1038/s41598-019-51704-w

209. Ono K, Eguchi T, Sogawa C, Calderwood SK, Futagawa J, Kasai T, et al. HSP70 enhances immunosuppressive function of CD4(+)CD25(+) T regulatory cells and cytotoxicity in CD4(+)CD25(-) T cells. *PloS One* (2012) 7(12):e51747–7. doi: 10.1371/journal.pone.0051747

210. Asea A, Kraeft SK, Kurt-Jones EA, Stevenson MA, Chen LB, Finberg RW, et al. HSP70 stimulates cytokine production through a CD14-dependent pathway, demonstrating its dual role as a chaperone and cytokine. *Nat Med* (2000) 6(4):435–42. doi: 10.1038/4697

211. Breloer M, Fleischer B, Bonin AV. In Vivo and In Vitro Activation of T Cells by Heat Shock Protein gp96 Induces Dendritic Cell Maturation and Antitumor Immunity. *J Immunol* (2001) 167(12):6731. doi: 10.4049/jimmunol.167.12.6731

212. Asea A. Initiation of the Immune Response by Extracellular Hsp72: Chaperokine Activity of Hsp72. *Curr Immunol Rev* (2006) 2(3):209–15. doi: 10.1074/jcri.20040720

213. Asea A. Chaperone-induced signal transduction pathways. *Exerc Immunol Rev* (2003) 9:25–33.

214. Albakova et al. HSPs in Lymphoma Immunotherapy.
and Oxidative Stress Management Functions. *Ann New York Acad Sci* (2007) 1100(1):306–11. doi: 10.1196/annals.1395.032

238. Wadhwa R, Takano S, Kaur K, Aida S, Yaguchi T, Kaul Z, et al. Identification and characterization of molecular interactions between mortalin/mtHsp70 and HSP60. *Biochem J* (2005) 391(Pt 2):185–90. doi: 10.1042/bj20050861

239. Custer CD, Kaul SC, Wadhwa R. On the Brotherhood of the Mitochondrial Chaperones Mortalin and Heat Shock Protein 60. *Cell Stress Chaperones* (2006) 11(2):116–28. doi: 10.1379/CSC-144R.1

240. Goetz MP, Toft DO, Ames MM, Erlichman C. The Hsp90 chaperone complex as a novel target for cancer therapy. *Ann Oncol* (2003) 14 (8):1169–76. doi: 10.1093/annonc/mdg316

241. Zhang H, Chung D, Yang Y-C, Neely L, Tsurumoto S, Fan J, et al. Identification of new biomarkers for clinical trials of Hsp90 inhibitors. *Mol Cancer Ther* (2006) 5(5):1256. doi: 10.1158/1535-7163.MCT-05-0537

242. Zhao M, Ding JX, Zeng K, Zhao J, Shen F, Yin YX, et al. Heat shock protein 27: a potential biomarker of peritoneal metastasis in epithelial ovarian cancer? *Tumor Biol* (2014) 35(2):1051–6. doi: 10.1007/s13277-013-1139-7

243. Suzuki K, Ito Y, Wakai K, Kawado M, Hashimoto S, Seki N, et al. Serum Heat Shock Protein 70 Levels and Lung Cancer Risk: A Case-Control Study Nested in a Large Cohort Study. *Cancer Epidemiol Biomarkers & Prev* (2006) 15 (9):1733. doi: 10.1158/1055-9965.EPI-06-0005

244. Gunaldi M, Afsar CU, Okuturlar Y, Gedikbasi A, Kocoglu H, Kural A, et al. Elevated Serum Levels of Heat Shock Protein 70 Are Associated with Breast Cancer. *Tohoku J Exp Med* (2015) 236(2):97–102. doi: 10.1620/tjem.236.97

245. Dunphy MPS, Press C, Pillarsetty N, Grkovski M, Modi S, Jhaveri K, et al. First-in-Human Trial of Epichaperome-Targeted PET in Patients with Cancer. *Clin Cancer Res* (2020) 26(19):5178. doi: 10.1158/1078-0432.CCR-19-3704

**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

*Copyright © 2021 Albakova, Mangasarova and Sapozhnikov. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.*