Diffuse large B-cell lymphoma (DLBCL) is the most common type of lymphoma in adults, characterized by a rapidly increasing painless mass. A novel compound, DCZ3301, was synthesized that exerted direct cytotoxicity against DLBCL cell lines. The effects of DCZ3301 on DLBCL cells in vitro and in vivo and the associated mechanisms were investigated. DCZ3301 inhibited the viability of DLBCL cell lines, even in the presence of protumorigenesis cytokines. Additionally, the compound induced apoptosis and cell cycle arrest at the G2/M phase by reducing mitochondrial membrane potential. DCZ3301 exerted an antitumor effect through modulation of Akt, extracellular signal-regulated kinases 1/2 (ERK1/2) and janus kinase 2 (JAK2)/signal transducer and activator of transcription 3 (STAT3) signaling pathways. Furthermore, DCZ3301 downregulates STAT3 phosphorylation by inhibiting Lck/Yes-related novel protein tyrosine kinase (Lyn) activation in DLBCL. A synergistic cytotoxic effect on DLBCL cells was observed upon combination of DCZ3301 with panobinostat. In vivo, intraperitoneal injection of xenograft mice with DCZ3301 resulted in reduced tumor volume. Our preliminary results collectively support the utility of the small-molecule inhibitor DCZ3301 as an effective novel therapeutic option for DLBCL that requires further clinical evaluation.

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Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of lymphoid cancer, accounting for ~30% of all lymphoma cases. DLBCL is a clinically and genetically heterogeneous lymphoid malignancy mainly characterized by two major molecular subtypes representing different stages of B-cell lymphoid differentiation based on gene expression profiling, specifically activated B-cell-like and germinal center B-cell-like. Although the current standard chemotherapy regimen of rituximab plus cyclophosphamide, vincristine, doxorubicin and prednisone (R-CHOP) for DLCBL patients can enhance response rates (RR) and prolong the survival of patients, >30% of patients still fail to respond or show relapse with resistant disease. Therefore, the development of novel drugs or therapies that can be effectively applied to improve the outcomes of DLBCL patients is an essential medical need.

The phosphatidylinositol 3-kinase (PI3K)/Akt/mTOR signal pathway is one of the most prominent pathways against malignant lymphoma, and PI3K/Akt inhibitors have been shown to be effective in DLBCL. Extracellular signal-regulated kinase 1/2 (ERK1/2) is a member of the mitogen-activated protein kinase family that regulates cell proliferation and survival associated with genomic instability. The ERK1/2 pathway is activated during apoptotic cell death of DLBCL. Signal transducer and activator of transcription 3 (STAT3) activated in B-cell lymphoma patients present an attractive target for therapeutic development with the potential of inhibiting cancer cell growth. Research on a large sample of DLBCL patients treated with R-CHOP showed that activation of the STAT3 signaling pathway is related to shorter survival. Furthermore, targeting the STAT3 pathway presents a potential approach to reverse CHOP resistance in patients with DLBCL. Lck/Yes-related novel protein tyrosine kinase (Lyn), belonging to Src tyrosine kinase family, is expressed preferentially in the membrane of B cells and other hematopoietic cells rather than T cells. The activation of Lyn, which leads to STAT3 phosphorylation, has an important role in B-cell activation in lymphoma cells.

In the present study, we showed that DCZ3301, a newly synthesized aryl-guanidino agent, exerts an antitumor effect via inhibiting proliferation of DLBCL cells, both in vitro and in vivo. Moreover, DCZ3301 induced apoptosis and cell cycle arrest by regulating Akt, ERK1/2 and STAT3 pathways in DLBCL cells without exerting cytotoxicity in normal cells. The antitumor activity of DCZ3301 in a mouse xenograft model and the molecular mechanisms underlying DCZ3301-mediated induction of apoptosis were further investigated. Our findings suggest that DCZ3301 can be effectively applied as a novel potential therapeutic regimen for DLBCL.
Results

**DCZ3301 inhibits DLBCL cell proliferation.** As shown in Figure 1a, DCZ3301 is a newly synthesized compound with a molecular weight of 464.0 Da. To investigate the efficacy of DCZ3301 in DLBCL, OCI-LY8, NU-DUL-1 SUDHL-4, DB and TMD8 cells were treated with DCZ3301 at concentrations of 1, 2, 4, 8, 16, and 32 μM. Proliferation of DLBCL cells was detected using the Cell Counting Kit-8 (CCK-8) assay. Treatment with DCZ3301 for 48 h resulted in a dose-dependent decrease in DLBCL cell proliferation (Figure 1b). The calculated half-maximal inhibitory concentration (IC50) values were as follows: 7.1 (OCI-LY8), 9.7 (NU-DUL-1), 8.67 (SUDHL-4), 8.04 (DB), and 9.66 μM (TMD8). DCZ3301 significantly inhibited the proliferation of DLBCL cells (OCI-LY8 and NU-DUL-1) in a time-dependent manner (Figures 1c and d). We further explored DLBCL proliferation by treatment with DCZ3301 in the presence or absence of interleukin-6 (IL-6) and insulin-like growth factor-1 (IGF-1), given that cytokines have an important role in lymphoma growth and survival. Although both IL-6 and IGF-1 alone can stimulate DLBCL cell growth, DCZ3301-induced growth inhibition was not influenced by these cytokines (Figures 1e and f).

**DCZ3301 induces apoptosis in DLBCL cells.** The apoptotic effect of DCZ3301 on DLBCL cells was examined via Annexin-V/propidium iodide (PI) double staining. Compared with the control group, apoptosis was distinctly induced in a time- and dose-dependent manner in OCI-LY8 and NU-DUL-1 cells by DCZ3301 (Figures 2a–d). These results were consistent with data obtained from the CCK-8 assay.

**DCZ3301 triggers a decrease in mitochondrial membrane potential.** Mitochondrial membrane potential (MMP), which
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Figure 2  DCZ3301 induces apoptosis in DLBCL cells. (a) OCI-LY8 cells were treated with DCZ3301 (4, 8, 12 and 16 μM) for 24, 48 and 72 h while (b) NU-DUL-1 cells were treated with DCZ3301 (5, 10, 15 and 20 μM) for 24, 48 and 72 h, double-stained with Annexin-V/propidium iodide (PI) and analyzed by flow cytometry. Columns show the percentage of Annexin-V positive cells from three independent experiments, data shown as the means ± S.D. (*P < 0.05; **P < 0.01, ***P < 0.001). (c) Analysis of OCI-LY8 and (D) NU-DUL-1 cells treated with certain concentrations of DCZ3301 at different time points (24, 48 and 72 h) were performed by Annexin-V/PI. The ratio of apoptotic cells is shown as means ± S.D. (*P < 0.05, **P < 0.01, ***P < 0.001)
participates in mitochondrial oxidative phosphorylation, is decreased prior to early pathological changes in the intrinsic pathway of apoptosis.\(^{20}\) To explore whether DCZ3301 affects mitochondrial depolarization, we used the JC-1 MMP detection kit to evaluate loss of MMP. Notably, relative to the control group, DCZ3301 treatment led to loss of MMP, in turn, activating the intrinsic apoptosis pathway, as shown in Figures 3a–c. Additionally, MMP reduction by DCZ3301 occurred in a time- and concentration-dependent manner.

**DCZ3301 treatment enhances caspase activation.** To further clarify the molecular mechanism underlying DCZ3301-induced apoptosis in DCBCL cells, we detected the presence of cleaved caspase-3, caspase-8, caspase-9, poly ADP-ribose polymerase (PARP) and mitochondrial apoptotic pathway proteins (Bcl-2 family) via western blotting. As shown in Figure 3d, treatment of OCI-LY8 and NU-DUL-1 cells (8 or 16 \(\mu M\)) with DCZ3301 caused dose-dependent increase in the cleaved forms of caspase-3, caspase-8 and caspase-9 as well as PARP, indicating that DCZ3301 induces apoptosis in DLBCL cells through both extrinsic and intrinsic pathways. Furthermore, Z-VAD-FMK, a pan-caspase inhibitor, suppressed apoptosis of DCZ3301-treated NU-DUL (Figures 3e and f) and OCI-LY8 cells (data not shown). Downregulation of Bcl-2 and Bcl-xL and, conversely, upregulation of Bax confirmed disruption of mitochondrial integrity by treating DCZ3301 at the proteomic level. In addition, DCZ3301 exerted no significant effect on normal peripheral blood mononuclear cells (PBMCs), even at a concentration of 40 \(\mu M\), compared with the control group (Figure 3g), supporting its safety for use as a therapeutic agent for DLBCL.

**DCZ3301 arrests the cell cycle at the G2/M phase in DLBCL.** In view of the finding that DCZ3301 induces apoptosis in DLBCL cells, we assessed its effect on the cell cycle, which is also associated with proliferation, using flow cytometry. After treatment of OCI-LY8 and NU-DUL-1 cells with DCZ3301, the percentage of cells in the G2/M phase accumulated significantly in a time-dependent manner in both cell lines (Figures 4a–c). To further elucidate the molecular mechanisms underlying DCZ3301 induction of G2/M phase arrest, we examined the protein levels of phospho-checkpoint kinase2 (p-CHK2), cell division cycle 25A (cdc25A), cdc25C, cyclinB1 and p21 via western blotting analysis. As shown in Figure 4d, DCZ3301 caused an increase in p21 and p-CHK2 protein expression. Meanwhile, the protein levels of cdc25A, cdc25C and cyclinB1, which has an important role in G2/M phase arrest, were decreased in DCZ3301-treated DLBCL cells.

Akt, ERK 1/2 and JAK2/STAT3 pathways are regulated in DCZ3301-induced apoptosis. We further assessed the expression patterns of molecules involved in several classic pathways via western blotting to determine the mechanism underlying DCZ3301-induced apoptosis. Upregulation of phosphorylated ERK1/2 and downregulation of phosphorylated Akt were enhanced in OCI-LY8 and NU-DUL-1 cells treated with DCZ3301 (Figure 5a). Additionally, the JAK2/STAT3 pathway was suppressed on account of decreased phosphorylated STAT3 and JAK2. The c-Myc oncogene, a prognostic factor of DLBCL,\(^{21}\) was also reduced by DCZ3301 in a dose-dependent manner. To explore the pathway involved in the process of DCZ3301 treatment, knockdown of STAT3 was performed via siRNA in OCI-LY8 and NU-DUL-1 cells (Figure 5b). The efficacy of DCZ3301 was enhanced in this group, compared with that of the negative control siRNA group (Figure 5c), suggesting that STAT3 downregulation has a functional role in DCZ3301-induced apoptosis in DLBCL cells. Together, we found that DCZ3301 induces cell apoptosis in DLBCL cells by regulating JAK2/STAT3 pathways.

**STAT3 phosphorylation is inhibited by Lyn activation in DLBCL.** Whereas STAT3 inactivation has an important role in DCZ3301-induced apoptosis, we investigated the oncogene upstream that induces STAT3 phosphorylation, such as tyrosine kinase Lyn and Syk.\(^{16,22}\) As shown in Figure 6a, we found that the phosphorylation (Y507) of tyrosine kinase Lyn, rather than Syk, was downregulated by DCZ3301 treatment in DLBCL cells. Furthermore, our results demonstrated that the decrease of phosphorylated Lyn was enhanced with the passing of time (Figure 6b), suggesting that DCZ3301 inhibits the phosphorylation of Lyn in both time- and dose-dependent manner in DLBCL cells. On the other hand, we surprisingly found that DCZ3301 decreases the tyrosine phosphorylation of STAT3 in a manner that is very similar to Lyn (Figure 6b), suggesting that Lyn and STAT3 phosphorylation are suppressed synchronously after DCZ3301 treatment at the protein level. To explore whether the interaction between Lyn and STAT3 involved in the antilymphoma effect induced by DCZ3301, we overexpressed Lyn in DLBCL cell lines by transfecting a recombination plasmid (Figure 6c) and treated with or without DCZ3301. Our current data showed that Lyn-overexpressing (Lyn-OE) cells exhibit much higher level of phosphorylated STAT3 than negative control cells (Figure 6d). In addition, the suppression of phosphorylated STAT3 was observed more in Lyn-OE cells than in negative control cells after DCZ3301 treatment for only 24 h (Figure 6d). Based on the collective findings, we propose that DCZ3301 promotes DLBCL cell apoptosis through
Figure 4  DCZ3301 arrests the cell cycle at G2/M phase in DLBCL cells. (a) OCI-LY8 cells and (b) NU-DUL-1 cells were treated with DCZ3301 (4 μM) for 8, 12 and 24 h, stained with PI and analyzed on flow cytometry. (c) The percentage of G0/G1, S and G2/M phase cells after control or DCZ3301 treatment at different time points (8, 12 and 24 h). Data are shown as mean ± S.D. (n = 3, *P < 0.05; **P < 0.01; ***P < 0.001). (d) OCI-LY8 and NU-DUL-1 cells were treated with DCZ3301 (4 and 8 μM) for 24 h. The protein levels of p-CHK2, cyclinB1, cdc25A, cdc25C, p21 and Actin were assessed by western blotting.
modulating STAT3 signaling by inhibiting Lyn activation.

**DCZ3301 inhibits tumor growth in vivo.** We further investigated the therapeutic efficacy of DCZ3301 in vivo by establishing a nude mouse xenograft model. Specifically, OCI-LY8 cells were injected into 6-week-old male BALB/c nude mice. Once the tumor volume reached the appropriate size, mice were treated with 5% dimethyl sulfoxide (DMSO) and saline or DCZ3301 via intraperitoneal injection. During the experimental period, volume, weight and the general state of all mice were measured every day to determine the antitumor effect and lethal toxicity or other side effects following DCZ3301 treatment. Administration of DCZ3301 induced a significant decrease in tumor growth (Figures 7a and b) while mouse weight was not significantly different between the DCZ3301-treated, 5% DMSO and saline groups (Figure 7c). Cell necrosis was observed via hematoxylin and eosin (H&E) and TUNEL staining in tumors of the DCZ3301-treated group, compared with those of the control group (Figure 7d). In addition, the expression of phospho-STAT3 in the tumor tissues was downregulated by DCZ3301 treatment (Figure 7d). During the process of drug administration, microscopic observation of functional organs revealed no evidence of growth disorder or organ dysfunction (data not shown). Our findings support the safety and efficacy of DCZ3301 as a promising novel treatment for lymphoma.

**DCZ3301 acts synergistically with panobinostat in DLBCL cells.** To ascertain whether DCZ3301 can be effectively used in combination therapy, we examined the proliferation of OCI-LY8 cells treated with increasing concentrations of DCZ3301 in conjunction with specific concentrations of panobinostat. Combination of DCZ3301 and panobinostat generally induced synergetic cytotoxicity in OCI-LY8 cells indicated by combination index \(<1.0\) for the most part (Figures 7e and f). Combination of DCZ3301 with the histone deacetylase inhibitor vorinostat led to a weak synergistic effect (data not shown).

**Discussion**

DLBCL is the most common lymphoma type in adults worldwide that presents a substantial clinical problem.\(^{23}\) Even
following standard chemotherapy with R-CHOP, > 30% patients undergo relapse/refractory issues. Effective chemotherapeutic agents are therefore urgently required to improve therapeutic outcomes.

DCZ3301, a novel aryl-guanidino compound synthesized in our laboratory, shows the activity in multiple cancer cell types, particularly hematological tumors. Here we investigated the antitumor effects of DCZ3301 on human DLBCL cells and the associated mechanisms. The inhibitory effects of DCZ3301 on DLBCL cell lines were induced through apoptosis as well as G2/M phase cell cycle arrest. Concomitantly, DCZ3301 exerted no significant toxicity in PBMCs. In a DLBCL xenograft mouse model, administration of DCZ3301 led to inhibition of neoplasm growth, consistent with in vitro data.

We further assessed inhibition of proliferation induced by DCZ3301 in a DLBCL cell model. Initially, a dose- and time-dependent cytotoxic effect was demonstrated in the human DLBCL cell lines OCI-LY8, NU-DUL-1, SUDHL-4, TMD8 and DB, with an approximate IC50 value of 8 μM after DCZ3301 treatment for 48 h. Recent studies have reported that deficiency of IL-6 protects against B-cell lymphomagenesis while serum IL-6 levels are associated with prognosis of DLBCL. Moreover, downregulation of IGF-1 led to reduced proliferation of DLBCL cell lines through inhibition of the IGF-1 receptor. In the current study, IL-6- and IGF-1-cultured cells were significantly increased compared with the control group, indicating a role of these cytokines in promoting disease progression. Interestingly, however, DCZ3301-induced cell cytotoxicity was not significantly weakened in the presence of IL-6 and IGF-1, suggesting that DCZ3301 blocks the proliferation-associated pathways triggered by these cytokines.

DCZ3301 induced apoptosis in a dose- and time-dependent manner in the apoptosis study, consistent with data obtained with the CCK-8 assay. Experiments performed to establish whether the antitumor effect of DCZ3301 is exerted via a caspase-dependent apoptotic pathway revealed caspase activation, as evident from the increased presence of the cleaved forms of caspase-8, caspase-9, caspase-3 and PARP. The data indicate that DCZ3301 induces apoptosis in OCI-LY8 and NU-DUL-1 cells via both extrinsic and intrinsic apoptotic pathways. Caspase-8 and caspase-9 are the two key proteins, respectively, activated in the extrinsic and intrinsic apoptotic pathways, together resulting in PARP and caspase-3 cleavage.
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DCZ3301 inhibits the growth of tumor in a xenograft mouse model and synergizes with panobinostat in DLBCL cell lines. OCI-LY8 cells (2.0×10⁶) were subcutaneously injected into the flank of 6-week-old nude mice and, respectively, administered 5% DMSO and saline to the controlled group or DCZ3301 (40 mg/kg) to the drug-treated group for 12 days (n=3/group). (a) The tumor samples were collected and imaged using a digital camera. (b) The tumor volume was measured each day for 12 days (P<0.05). (c) The weight of mice was measured each day for 12 days. (d) H&E, TUNEL and anti-phospho-STAT3 antibody staining of tumor tissues from controlled or DCZ3301-treated mice were pictured (original magnification: ×400). (e) OCI-LY8 cells were treated with panobinostat or panobinostat at a constant concentration of DCZ3301 or (f) were treated with DCZ3301 or DCZ3301 at a constant concentration of panobinostat and then the cell proliferation was detected using CCK-8 assay after culturing for 48 h.

Data analyzed by the Calcsyn software shows the synergistic activity of DCZ3301 and panobinostat against DLBCL cell lines. OCI-LY8 cells were treated with panobinostat or panobinostat at a constant concentration of DCZ3301 or (f) were treated with DCZ3301 or DCZ3301 at a constant concentration of panobinostat and then the cell proliferation was detected using CCK-8 assay after culturing for 48 h. Data analyzed by the Calcsyn software shows the synergistic activity of DCZ3301 and panobinostat against DLBCL cell lines. Combination index <1 indicates synergy.
triggered by Lyn phosphorylation. Synergistic effects on DLBCL cells were exerted by a combination of DCZ3301 and panobinostat. Consistent with in vitro results, DCZ3301 inhibited tumor growth in vivo with decreased phospho-STAT3. Our collective findings suggest that DCZ3301 may be applied as a potential therapy to improve outcomes in DLBCL patients. However, the detailed mechanisms and clinical effects of DCZ3301 in DLBCL require further research.

Materials and Methods

Cell culture. The human cell lines, OCI-LY8 and NU-DUL-1, were a kind gift from Professor Xiaoyan Zhou from the Department of Pathology of Fudan University Shanghai Cancer Center (Shanghai, China). MB-2 and SUDHL-4 cell lines were purchased from American Type Culture Collection (ATCC) (Manassas, VA, USA). The TMD8 cell line was acquired from Professor Dongsheng Xu (Shanghai Tenhang People's Hospital, Tongji University of Medicine, Shanghai, China). Human OCI-LY8 cells were cultured in Iscove’s Modified Dulbecco’s Medium (Gibco, Life Technologies, Carlsbad, CA, USA) supplemented with 10% fetal bovine serum (FBS, Gibco) and 1% penicillin-streptomycin (Gibco), while all other cell lines were cultured in RPMI 1640 (Gibco) containing 10% FBS and 1% penicillin-streptomycin. All cells were incubated in a humidified atmosphere at 37 °C in 5% CO2. Normal PBMCs isolated from human peripheral blood provided voluntarily using Lymphoprep (Stemcell Technologies, Vancouver, Canada) were cultured in RPMI 1640 containing 10% FBS. Informed consent was obtained from each volunteer. These studies were approved by the institutional review board of Shanghai Tenhang People’s Hospital (Shanghai, China).

Reagents. A 16 mM DCZ3301 stock solution was dissolved in DMSO (Sigma, St. Louis, MO, USA) and stored at −20 °C. Antibodies for ERK1/2, phospho-ERK1/2, Akt, phospho-Akt, STAT3, phospho-STAT3, Lyn, phospho-Lyn, Syk, phospho-Syk, JAK2, phospho-JAK2, cleaved Caspase-8, Bax, B cell lymphoma-2 (Bcl-2), Bcl-xL, PARP, c-Myc, p21 and Actin (for western blotting) were purchased from Cell Signalling Technology (Danvers, MA, USA). Caspase-9, cleaved caspase-3, p-STAT3, p-Akt, p-ERK1/2, p-Lyn, cyclinB1 antibodies were purchased from Abcam (Cambridge, MA, USA). IL-6 and IFG-1 (R&D Systems, Minneapolis, MN, USA) dissolved in phosphate-buffered saline (PBS) containing 0.1% albumin from bovine serum albumin (BSA) were prepared of nude mice. After tumor size had reached an approximate volume of 100 mm3, six mice were randomly divided into control (5% DMSO and saline only) and DCZ3301-treated groups (40 mg/kg DCZ3301 in 5% DMSO and saline) (n = 3/group). Mice were monitored for tumor size and weight each day. At the end of the experimental period, all mice were killed, and the tumors were obtained and imaged. Tumors of mice were embedded in paraffin after imaging, and H&E, TUNEL and anti-STAT3 antibody staining of 5-μm-thick sections of tumors and livers was performed. All animal-related procedures were approved by the Animal Care and Use Committee of The Tenhang People’s Hospital (Shanghai, Tongji University). This research was approved by the Science and Technology Commission of Shanghai Municipality (ID: SYXK 2011-0111).

Statistical analysis. Data are expressed as means ± S.D. Comparisons among the experimental groups were conducted with Students t-test, and the significance of multiple comparisons was determined using one-way ANOVA. All statistical analyses were performed with the SPSS v20.0 statistical analysis software (IBM Corp., Armonk, NY, USA). A P value of ≤ 0.05 was considered significant.

Conflict of Interest

The authors declare no conflict of interest.

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