Minireview

Non-Hodgkin's B-cell lymphoma: Advances in molecular strategies targeting drug resistance

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Abstract

Non-Hodgkin's lymphoma (NHL) is a heterogeneous class of cancers displaying a diverse range of biological phenotypes, clinical behaviours and prognoses. Standard treatments for B-cell NHL are anthracycline-based combinatorial chemotherapy regimens composed of cyclophosphamide, doxorubicin, vincristine and prednisolone. Even though complete response rates of 40–50% with chemotherapy can be attained, a substantial proportion of patients relapse, resulting in 3-year overall survival rates of about 30%. Relapsed lymphomas are refractory to subsequent treatments with the initial chemotherapy regimen and can exhibit cross-resistance to a wide variety of anticancer drugs. The emergence of acquired chemoresistance thus poses a challenge in the clinic preventing the successful treatment and cure of disseminated B-cell lymphomas. Gene-expression analyses have increased our understanding of the molecular basis of chemotherapy resistance and identified rational targets for drug interventions to prevent and treat relapsed/refractory diffuse large B-cell lymphoma. Acquisition of drug resistance in lymphoma is in part driven by the inherent genetic heterogeneity and instability of the tumour cells. Due to the genetic heterogeneity of B-cell NHL, many different pathways leading to drug resistance have been identified. Successful treatment of chemoresistant NHL will thus require the rational design of combinatorial drugs targeting multiple pathways specific to different subtypes of B-cell NHL as well as the development of personalized approaches to address patient-to-patient genetic heterogeneity. This review highlights the new insights into the molecular basis of chemorefractory B-cell NHL that are facilitating the rational design of novel strategies to overcome drug resistance.

Keywords: Drug resistance, NHL, B-cell lymphoma, mechanisms of drug resistance, Akt, apoptosis, NFκB, oxidative stress, microRNAs, TGFβ, cluster differentiation antigens, multidrug resistance, drug metabolism, MAP kinases, tyrosine kinases, p53, proteasome, epigenetics, microsatellite instability, stromal influences, stroma, sphingosine kinase, geranylation, zinc transporter, positive regulatory domain I protein, retinaldehyde dehydrogenase

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Introduction

The problem of multidrug resistance in non-Hodgkins lymphoma

Non-Hodgkins lymphoma (NHL) is a heterogeneous class of cancers displaying a diverse range of biological phenotypes, clinical behaviours and prognoses. The majority of NHL cases originate from B cells with about 10% arising from T cells.[1,2] B cells that normally undergo clonal expansions at different stages of differentiation can give rise to the B cell type of NHL.[3]

The standard treatment for NHL is the anthracycline-based chemotherapy regimen, termed CHOP, which is composed of cyclophosphamide, doxorubicin, vincristine and prednisolone.[4] The addition of rituximab (*monoclonal antibody to CD20*) to CHOP (*R-CHOP*) has provided the first major improvement in therapy in over three decades and is now the new standard for treatment.[5] Most NHL patients initially respond to chemotherapy yielding complete response rates of 40–50%.[6–10] Regrettably, a substantial population of patients undergo relapse, resulting in disappointing 3-year overall survival rates of only about 30%.[11] The problem is compounded by the higher doses of CHOP administered to relapsed patients, which have resulted in severe side-effects and a response in only about one-third of relapsed patients.[12–14] Relapsed lymphomas are not only refractory to subsequent treatments with the initial chemotherapy regimen but also can exhibit cross-resistance to a wide variety of anticancer drugs.

Acquisition of chemoresistance in B-cell lymphomas is due to the emergence of subpopulations of drug-resistant tumour cells, which leads to the failure of standard

CHOP therapies. Chemoresistance in NHL is not consistently associated with the upregulation of multidrug pump (i.e. P-glycoprotein; MDR1) expression indicating the existence of other drug-resistant mechanisms.[15,16] Inherent genetic heterogeneity and instability of the tumour cells drive the acquisition of drug resistance in lymphoma.[17]

It is now apparent that a new generation of less toxic and more targeted approaches based on rational drug design is needed to prevent and/or reverse chemoresistant disease.[18] The purpose of this article is to highlight the many new insights into the molecular basis of chemorefractory NHL, which are leading the way to the rational design of novel drugs to overcome chemoresistance. Due to the genetic heterogeneity of B-cell NHL, many different pathways leading to drug resistance have been identified. Successful treatment of chemoresistant NHL will thus require cocktails of combinatorial drugs targeting multiple pathways specific to different subtypes of NHL as well as the development of personalized approaches to address patient-to-patient genetic heterogeneity.

Innate and acquired drug resistance varies among subtypes of NHL

Aggressive NHL includes diffuse large B-cell lymphoma (DLBCL), mantle-cell lymphoma (MCL), Burkitt's lymphoma (BL), follicular lymphoma (FL) and peripheral T-cell lymphoma (PTCL). Each of these subtypes of NHL display a wide range of responses and outcomes to standard chemotherapeutic regimens due to genetic heterogeneities. Despite remarkable advances in chemotherapy, more than half of patients with aggressive B-cell NHL (B-NHL) are incurable.[6] PTCL, in particular, remains a challenge for chemotherapy since there are no drugs that can prevent progression of the disease.[19]

The two most common types of NHL are DLBCL and FL, representing more than half of all patients with B-NHL.[1] The most common histological type is DLBCL and is classified as an aggressive subtype, but potentially is curable with chemotherapy.[1,20–22] The second most frequent type of NHL is FL, which is usually incurable with conventional chemotherapy, and exhibits a median survival of 10 years postdiagnosis.[23] MCL is an aggressive disease with a 3–4-year median survival and poor responsiveness to conventional chemotherapy.[24–27]

Drug-resistant DLBCL

Most DLBCL patients initially respond favourably to CHOP, but ~50% eventually relapse with CHOP-resistant disease that disseminates and is highly lethal without transplantation.[28] Even though CHOP-resistant DLBCL affects about 10,000 new cases in USA each year, the molecular features of CHOP-resistant DLBCL have not been adequately defined. Drug resistance can be inherent (innate) from the beginning[29] or develop from prior exposure to chemotherapy (acquired).[30,31] The varied responses of DLBCL to chemotherapy are due to aberrations in multiple molecular pathways, which are attributed to the heterogeneous genetic nature of DLBCL.[32] Gene expression profiling (GEP) of patient tumours has better defined the molecular heterogeneity underlying the heterogeneous clinical behaviour of DLBCL. Patients with DLBCL have been classified into three groups according to their GEP patterns based on the three cell-of-origin signatures, activated B-cell–like DLBCL (ABC-DLBCL), germinal-centre B-cell–like DLBCL (GCB–DLBCL) and mediastinal.[33–36] The GCB and ABC subcategories are characterized by distinct differences in survival, chemoresponsiveness and dependence on signalling pathways.[37] ABC–DLBCL resembles *in vitro* activated B cells. In a separate multiple clustering array analysis,[38] DLBCLs were categorized into Ox-phos, BCR/proliferation and host-response signatures. The BCR/proliferation subset displayed the upregulation of genes involved in B-cell activation and proliferation.

Mantle-cell lymphoma

Mantle-cell lymphoma (MCL) is an aggressive disease that has a poor response to conventional chemotherapy resulting in an overall survival of about 3–4 years.[27,39] A major problem in treating MCL is the occurrence of relapse caused by resistance to chemotherapy. Many different drug combinations comprised of alkylating agents, anthracyclines and purine analogs have been tested in MCL patients.[40]

One of the unique features of MCL is a cluster differentiation (CD) phenotype associated with a specific chromosomal translocation, t(11;14)(q13;q32), which translocates the cyclin D1 gene to be under the control of the immunoglobulin heavy chain gene enhancer, resulting in upregulation of cyclin D1.[41] Overexpression of cyclin D1 plays a critical role in the pathogenesis and chemorefractoriness of MCL. However, accumulating evidence indicates that MCL frequently is dysregulated not only in cell-cycle regulation but also in apoptosis and DNA repair.[42,43]

MCL frequently can also be innately resistant to anticancer agents.[43] A number of dysfunctional biochemical pathways have been identified that may contribute to the relatively high resistance of MCL to chemotherapy-induced apoptosis,[44] including the activation of NFκB pathway,[45–47] overexpression of antiapoptotic proteins and the absence of proapoptotic proteins.[48] GEP has also identified the upregulation of genes associated with multidrug resistance in MCL.[49] The resistance of MCL to alkylating agents and to anthracycline can also result from the upregulation of the glutathione *S*-transferase (GST) gene, which is located in 11q13 and thus co-amplified along with the cyclin D1 gene[50] as well as the phosphoinositide 3-kinase/Akt pathway (PI3K/Akt).[51,52] Despite the generation of several new therapeutic agents directed against PI3K/Akt, B-cell receptor signalling and Bcl-2, poor clinical outcomes continue to be a problem in a significant population of MCL patients.[43,53]

Drug-resistance pathways in B-cell NHL

PI3K/Akt pathway in B-cell NHL drug resistance

The PI3K/Akt pathway plays a central role in promoting survival and chemoresistance in NHL.[54–58] Dysregulation of the PI3K/Akt pathway is frequent in DLBCL and worsens prognosis.[58–65] New drugs targeting this pathway have

shown encouraging results in treating relapsed NHL patients.[66–71] However, not all chemorefractory DLBCL patients show positive responses to current Akt pathway inhibitors, and many experience severe side-effects.[72,73]

A primary mediator of PI3K signalling is the Akt/protein kinase B kinase, which acts to promote cell survival through direct phosphorylation of apoptotic regulators. Akt phosphorylation of proapoptotic substrates (including Bad, FOXO, GSK-3β and ASK1) targets them for binding to 14-3-3 proteins,[74–80] which effectively neutralizes their ability to induce apoptosis.

A role for the activation of the Akt pathway in promoting chemoresistance in NHL was shown by treatment with pharmacological inhibitor (LY-294002) and by Akt siRNA, both of which inhibited Bcl-xL expression and sensitized the cells to chemotherapeutics.[81] Moreover, higher Akt activity was observed in CHOP-resistant DLBCL cells than in CHOP-sensitive cells, which was associated with the upregulation of 14-3-3ζ.[82,83] Chemical inhibition of Akt[82] or shRNA-mediated knockdown of 14-3-3ζ[83] restored CHOP sensitivity to the resistant cells, indicating that CHOP resistance was mediated by these proteins, was reversible and might be targeted as a clinical strategy for CHOP resensitization.

mTOR in the Akt pathway is an important therapeutic target for DLBCL. Rapamycin inhibited mTORC1 in DLBCL lines and primary tumours with minimal cytotoxicity.[84] Clinical trials of the rapamycin analogs, temsirolimus and everolimus have demonstrated overall response rates of about 30% for relapsed DLBCL.[85–87] However, only about half of relapsed patients respond to mTOR inhibitors. A critical focus needs to be on the development of new inhibitors of the PI3K/Akt pathway that bypass resistance mechanisms. As an example, addition of a histone deacetylase inhibitor reversed resistance to rapamycin.[84]

Dysregulated apoptotic pathways

The germinal centre (GC) is the location of immune surveillance in the lymph node. B cells that express functional B-cell receptors and have a block to execution of an activated apoptotic program migrate to the GC.[88] One hallmark of germinal centre-derived B-cell NHL (GC-DLBCL) is resistance to apoptosis characterized by the dysregulation of apoptotic control mechanisms.[37,89,90] In addition, dysregulation of genes involved in apoptotic pathways has also been reported to be associated with chemoresistance in activated B-cell-like DLBCL (ABC-DLBCL). Thus, a promising approach in both frontline and salvage therapeutic strategies in B-cell NHL is targeting altered apoptotic pathways. Strategies targeting the two main apoptotic pathways, extrinsic and intrinsic, are summarized below.

Extrinsic (death receptor) pathway

The tumour-necrosis factor receptor (TNFR) family of transmembrane proteins, including the death receptors for Fas (CD95) and tumour necrosis factor-related apoptosis-inducing ligand (TRAIL), induces cell death. TRAIL mediates apoptosis by binding to cell-surface transmembrane receptors, either death receptor 4 (DR4/APO2/TRAIL-R1) or death receptor 5 (DR5/KILLER/TRAIL-R2/TRICK2),[91] which recruit the death-inducing signalling complex composed of FADD and the inactive proenzymatic form of the apoptosis-initiating proteases caspase-8.[92,93] Self-activation of caspase-8 by autoproteolysis leads to the activation of the executioner caspase-3 to carry out apoptosis.

TNFR family members can selectively induce apoptosis in some drug-resistant B-cell lymphomas.[94–97] Twelve out of 22 primary lymphoma cell cultures derived from biopsied DLBCL samples were sensitive to TRAIL,[97] which included seven clinically chemoresistant lymphomas. TRAIL was found to induce apoptosis in DLBCL cells expressing the upregulation of prosurvival molecules, Bcl-2 and/or X-linked inhibitor of apoptosis (XIAP). Thus, TRAIL might be an effective therapy for drug-resistant DLBCL patients that show dysregulated extrinsic apoptosis pathways.[96,98,99]

The Bfl-1 protein is required for the survival of malignant B cells and might be a potential target against drug-resistant B-cell lymphoma.[100] Bfl-1 is a direct transcriptional target of nuclear factor-kappa B (NF-κB),[101–103] and its upregulation is associated with an increased resistance to tumour-necrosis factor (TNF)-α, anti-CD95, TRAIL and chemotherapeutic drugs.[102–104] In DLBCL, downregulation of Bfl-1 occurs in tumour cells induced to undergo apoptosis by inhibition of the activated NF-κB pathway.[105] Moreover, short-hairpin RNA silencing of Bfl-1 in DLBCL cell lines sensitized those cell lines to anti-CD20 (rituximab)-mediated cell death and chemotherapeutic agents. Thus, Bfl-1 will be a candidate target in the design of new strategies for drug-resistant cancer therapy.

Intrinsic pathway

The Bcl-2 family regulates an apoptotic pathway that is initialized at the mitochondrion known as the intrinsic apoptotic pathway. Bcl-2 family members function through mutual interactions with each other and the balance between the anti-apoptotic (Bcl-2, Bcl-xL, Mcl-1) and the proapoptotic (Bax, Bak; and the BH3-only Bid, Bim and PUMA protein) members are critical for preventing or initiating apoptosis.[106,107] The BH3-only proapoptotic (Bid, Bim, PUMA) proteins act as molecular sensors of cellular stress or damage and are activated in response to DNA damage, growth factor withdrawal and oncogene activation.[108]

Many chemotherapeutic drugs activate the intrinsic apoptosis pathway, leading to the release of proapoptotic molecules, including cytochrome *c*, from the intermembrane space of mitochondria into the cytosol. Cytochrome *c*, Apaf-1 and procaspase-9 complex together to form the apoptosome machinery in the cytoplasm. The apoptosome promotes oligomerization of Apaf-1, which then triggers the activation of the initiator procaspase-9. The active caspase-9, in turn, cleaves and activates downstream executioner caspases, including pro-caspase-3, which cleaves proteins, thus producing the characteristic apoptotic phenotype of blebbing, nuclear condensation and cell shrinkage.

Dysregulation of apoptosome formation and caspase activation has been associated with chemoresistance in B-cell lymphoma. BL cells commonly are resistant to

apoptosis induction by chemotherapeutic agents, which has been attributed to deficient levels of Apaf-1, thus leading to the failure of cytochrome *c* to promote apoptosome formation and caspase activation.[109]

Overexpression of antiapoptotic family members in B-cell lymphomas is associated with the inhibition of apoptosis and chemotherapy resistance, resulting in lower clinical response rates and shortened survival.[110–114] Bcl-2 was observed overexpressed in about 80% of FL and 20% of DLBCL as a result of the t(14;18) translocation and amplification of the Bcl-2 gene, respectively.[115–117] Bcl-2 expression was also correlated with a higher relapse-rate, shorter disease-free survival and shorter overall survival.[16,118–121] Antisense-mediated repression of Bcl-2 expression resulted in significant increases in the sensitivity of lymphoma cells to chemotherapeutic drugs.[122–124] Oblimersen (Genta Inc.) is a phosphorothioate Bcl-2 antisense oligonucleotide, which in combination with rituximab, resulted in an overall response rate of 42% including 10 complete responses and 8 partial responses in relapsed B-cell NHL patients.[125] Median duration of response was 12 months with minimal toxicities. Thus, co-administration of Oblimersen and rituximab is a safe treatment that will be most beneficial in patients with refractory NHL.

IAP proteins

Inhibitor of apoptosis (IAP) proteins can block executioner caspases.[126] Overexpression of IAPs (XIAP) has been shown to result in resistance to agents that induce apoptosis pathways.[127,128] XIAP is the most potent inhibitor of the apoptosis cascade and can repress apoptosis induced by TNF, TRAIL, Fas-L and conventional chemotherapeutics.[127,128] In DLBCL, XIAP expression was associated with a poor prognosis.[129] A small-molecule XIAP antagonist re-activated the intrinsic apoptosis pathway in drug-resistant DLBCL cell lines.[130,131] Peripheral blood mononuclear cells and tonsil germinal-centre B cells from healthy donors were not affected, validating the XIAP antagonist for possible development as a therapy for chemotherapy-refractory DLBCL. The sensitivity of DLBCL cells to the XIAP antagonist could be predicted from molecular markers, such as expression of XIAP, Bcl-2 and levels of constitutive caspase-9 activation,[131] indicating a potential for selecting patients for XIAP therapy.

DNA damage response

Mutations in the DNA damage response (DDR) genes may promote tumour formation as well as drive emergence of drug resistance. The *Atm* gene product is a primary component of the DDR, which has a phosphatidylinositol-3-kinase-like protein kinase that phosphorylates many proteins upon DNA damage.[132] Atm mutations have identified in hematologic malignanices.

An association between Myc activation and Atm inactivation has been identified during the progression of human B-cell lymphomas.[133] In mice, *Atm* loss collaborated with Myc activation to accelerate the development of lymphomas.[134–136] Following anticancer therapy, *Atm* (DDR)-compromised lymphomas exhibited defects in ability to undergo apoptosis and had a poorer long-term outcome as compared to DDR-competent lymphomas. *Atm* thus appears to prevent tumour progression by converting oncogenic signalling into apoptosis, resulting in selection against an *Atm*-dependent DDR and the emergence of drug-resistant lymphomas.

NFκB pathway

Activation of NF-κB is a driver in apoptosis resistance in a variety of B-cell malignancies leading to poor outcome in lymphoma patients.[137,138] The NF-κB family has the capacity to regulate transcription of a diverse array of genes involved in cancer cell growth, including those involved in proliferation and resistance to apoptosis.[139–142] Drug-resistant lymphoma cell lines have been sensitized by treatment with inhibitors of the NF-κB pathway.[143,144]

Bfl-1 is a direct transcriptional target of NF-κB,[101–103] and its upregulation is associated with decreased sensitivity in lymphomas to chemotherapeutic drugs and apoptotic stimuli, including TNF-α and anti-CD95.[102–104] Inhibition of NF-kB pathway in DLBCL[37,105] led to the downregulation of Bfl-1 expression and apoptosis. Knockdown of Bfl-1 in sensitized DLBCL cell lines to anti-CD20 (rituximab) and standard chemotherapeutics.[100]

microRNAs

A microRNA, miR-21, has been shown to influence sensitivity of DLBCL cells to CHOP by impacting the PI3K/Akt-signalling pathway.[145] Mir21 targets PTEN for downregulation and NFκB upregulates miR-21. Knockdown of NFκB decreased miR-21 and sensitized DLBCL cells to chemotherapy.

A frequent genetic alteration that has been observed in MCL is chromosome 13q31–q32 amplification targeting a microRNA cluster termed miR-17–92.[146–148] Upregulation of miR-17–92 activated the PI3K/AKT pathway and inhibited apoptosis induced by chemotherapeutics in MCL cell lines.[149] Downregulation of miR-17–92 repressed the PI3K/AKT pathway and inhibited tumour growth in a xenograft MCL mouse model.

TGFβ pathway

Members of the transforming growth factor-β (TGF-β superfamily modulate proliferation, apoptosis and differentiation in many different cell types. TGF-β inhibits cell proliferation by arresting cells in the G1 phase of the cell cycle through the p15INK4b, p21Cip1/WAF1, p27 and c-Myc proteins.[70] Binding of TGF-β receptors to their ligands activates the serine/threonine kinase activity of the TGF-β receptors (TβRI and TβRII). The ligand-activated TβRII phosphorylates and activates the TβRI, which in turn transmits the TGF-β signal by phosphorylating and activating the Smad2 and Smad3 proteins. The activated Smads oligomerize with Smad4, and the complexes then translocate to the nucleus where they regulate transcription of TGF-β target genes.[66,67,150]

Lymphoma cells can acquire resistance to TGF-β through promoter methylation of the TβRII gene.[71] Promoter

analysis in lymphomas revealed CpG methylations at −25 and −140 of the *TβRII* promoter that correlated with the silencing of the *TβRII* gene.

Overexpression of BCL6 contributes to TGF-β resistance in B-cell lymphoma. BCL6 transcriptionally represses Smad4.[72] B-cell lymphoma cells with upregulated BCL6 were refractory to TGF-β, whereas knockdown of BCL6 expression restored the response to TGF-β.

Oxidative stress pathways

Changes in oxidative stress pathways may explain the more aggressive tumour phenotype of drug-resistant lymphoma variants. In a murine lymphoma model, lymphoma cells transfected with catalase or selected for resistance to hydrogen peroxide were resistant to CHOP.[151–153] Oxidative stress-resistant cells demonstrated an altered metabolic profile, including the ability to generate ATP from alternative carbon sources such as glutamine.[154,155] When treated with glucocorticoids, the oxidative stress-resistant cells were better able to maintain ATP levels as compared to sensitive parental cells.[155] Experiments with an uncoupler of mitochondrial respiration showed that the oxidative stress-resistant cells produced more ATP from mitochondria than the sensitive cells.[154]

Reactive oxygen species

Once inside the cell, anthracyclines in the CHOP cocktail kill lymphoma cells by DNA intercalation, topoisomerase II inhibition and reactive oxygen species (ROS) induction. The type of ROS generated can be critical; superoxide anion and hydrogen peroxide inhibited cancer cell migration and invasion, whereas hydroxyl radical promoted cell migration and invasion.[156] The Akt-survival pathway has been implicated in regulating ROS in lymphoma cells. Akt activation correlated with both decreased ROS and increased cell survival in lymphoma cells.[157]

Chronic ROS exposure can generate lymphoma cells with upregulated antioxidant defense systems, which results in chemoresistance.[158] Oxidative stress-resistant variants expressed increased catalase and superoxide dismutase activities and increased phase 2 enzymes, NAD(P)H:quinone oxidoreductase and GSTs μ and π.

Proton pumps

The acidity of the tumour microenvironment due to hypoxic conditions, which influence ROS production, plays an important role in tumour progression, chemoresistance and metastatic behaviour.[159,160] Cancers adjust to acidity by upregulating proton extrusion activity, thus allowing the tumour cells to survive.[161–163] Tumour cells control intracellular pH through proton pumps like the vacuolar-type H+ ATPase (V-ATPase). Modification of cellular pH gradients by treatment with proton pump inhibitors (PPIs) sensitized B-lymphoma cells to chemotherapeutics through ROS production.[164] Neutralization of ROS by the antioxidant, *N*-acetylcysteine, delayed apoptosis. PPIs also inhibited the growth of B-cell lymphoma in SCID mice. Thus, PPIs may provide for therapeutic approaches for drug-resistant B-cell lymphomas.

GSH

The glutathione-*S*-transferases (GSTs) multigene family of enzymes detoxify electrophilic xenobiotics, including alkylating agents, and reduce oxidative stress.[165–171] Overexpression of the GST-π isoenzyme has been associated with alkylating agent and anthracycline resistance in lymphomas.[171]

CD antigens

CD20-rituximab. The coadministration of rituximab to CHOP chemotherapy has significantly increased the survival of DLBCL patients.[172–179] Rituximab is a humanized monoclonal antibody that binds to the CD20 antigen on B lymphocytes.[180] CD20 is expressed by >99% of B-cell NHL,[2] which is not internalized following antibody binding[181] or secreted into the circulation.[182] However, given that it is also expressed by normally differentiated pre-B cells and B cells,[183,184] normal B cells are also depleted during rituximab therapy, so that NHL patients have a prolonged B-lymphopenia following rituximab therapy.[185] Regrettably, many patients will relapse after rituximab/CHOP (R-CHOP) therapies.[184,186–193]

Rituximab exerts its antilymphoma activity through multiple mechanisms, including growth inhibition, apoptosis, complement-dependent cell cytotoxicity (CDC) and antibody-dependent cellular cytotoxicity (ADCC).[60,184] Although rituximab mediates CDC and ADCC of CD20-positive human B cells,[194] it can have direct apoptotic effects. Unfortunately, resistance to rituximab can eventually evolve in some patients during the course of disease, which is only explained in part by the loss of CD20 expression.[195]

A variety of signalling events have been observed in lymphoma cells exposed to rituximab *in vitro*, including the activation of Src-family of protein tyrosine kinases, decreased NFκB activity and downregulation of Bcl-2 levels.[196–201] Rituximab inhibited Akt in B-cell lymphoma cell lines, which contributed to the sensitization of drug-resistant cells to chemotherapeutic drugs.[81]

B-lymphoma cell lines resistant to rituximab have cross-resistance to multiple chemotherapeutic agents and exhibit downregulation of the Bcl-2 family proteins Bax and Bak.[202] Repeated exposure to rituximab generates a therapy-resistant phenotype by modulating the expression of Bax and Bak. The development of new inhibitors of the Akt and Bcl-2 pathways will now allow rationally designed clinical trials addressing Rituximab resistance that employ combinations of the new inhibitors and rituximab.

CD147. Upregulation of extracellular matrix metalloproteinase inducer (EMMPRIN or CD147) drives lymphoma progression and induces resistance to chemotherapeutic drugs.[203–208] CD147 is a transmembrane glycoprotein of the immunoglobulin superfamily that is expressed on the surface of lymphoma cells. It functions as a regulator of matrix metalloproteinase (MMPs) expression in the local

lymphoma environment.[204] High expression of MMPs has been correlated with tumour metastasis.[209] Reduced CD147 expression led to reduced metastasis and sensitized drug-resistant cells to chemotherapeutics.[210]

MDR proteins

The ability of cancer cells to resist the cytotoxic effects of chemotherapeutic agents is termed multidrug resistance (MDR), which is manifested by a decreased sensitivity to a wide range of nonhomologous drugs targeting multiple diverse pathways.[211] Overexpression of the 170–180 kDa ATP-dependent pump, P-glycoprotein (P-gp transporter), is frequently associated with resistance against a wide range of chemotherapeutics[212–215] and results in the MDR phenotype. P-gp transports or effluxes chemotherapeutics out of the cell, which reduces the intracellular concentration of the drugs, thus protecting cellular structures from damage and promoting cell survival. MDR due to the upregulated expression of P-gp product has been implicated as a critical factor in the prognosis and clinical outcome of refractory lymphoma patients.[215–218] Expression of P-gp has been found in all histological types of NHL.[219] Clinical trials combining chemotherapy with resistance modifiers have provided evidence for the role for P-gp in drug resistance in NHL.[220–222] However, some reports have indicated a lack of correlation between clinical response and P-gp expression,[29,216,223–225] possibly because MDR is mainly implicated in acquired drug resistance in lymphomas.[226,227] Thus, upregulation of P-gp is not consistently associated with chemoresistance in NHL, indicating the existence of additional drug-resistant pathways and mechanisms.[15,16]

Upregulation of the PI3K/Akt pathway can influence MDR in lymphoma. PI3K/Akt inhibition correlates with downregulation of NFκB activity and reduced Pgp function.[228] PI3K/Akt activity was higher in drug-resistant lymphoma cell lines than in sensitive cells, and PI3K/Akt inhibitors inhibited P-gp function and increased sensitivity to chemotherapeutics in drug-resistant cell lines.

Upregulation of the adenosine triphosphate-binding cassette drug transporter, ABCG2, in DLBCL correlated inversely with the disease-free survival.[229] Activated hedgehog (Hh) signalling stimulated high-ABCG2 expression in DLBCL through direct upregulation of ABCG2 gene transcription.[230] Activation of Hh signalling in DLBCL cell lines led to co-upregulation of Bcl-2 and ABCG2, which was associated with increased resistance to chemotherapeutics.

In addition to P-gp, the lung-resistance protein (LRP) is associated with MDR in lymphoma. LRP was first identified in a non-P-gp-multidrug-resistant lung cancer cell line.[231] LRP is the major protein component of vaults, which are complex ribonucleoprotein particles located primarily in the cytosol and nuclear membrane and mediate nucleocytoplasmic transport.[232,233] Upregulation of LRP is associated with resistance to multiple chemotherapeutics.[234,235] High LRP expression was associated with more aggressive lymphomas and a lower response rate to chemotherapy than LRP-negative patients.[236]

Drug metabolizing pathways

GSTs detoxify electrophilic chemotherapeutics, such as alkylating agents.[166–171] GSTs act by promoting direct binding of drugs to alkylating agents and steroids and can also neutralize free radicals generated by anthracyclines.[166,168,237–239] Drug resistance in lymphoma has been associated with an increase in glutathione content or GST activity.[167,171,240–242] The GST-π isozyme is elevated in lymphoma cell lines resistant to anticancer agents.[166–170] GST-π expression has been reported to have prognostic significance in DLBCL.[243]

Glutathione *S*-transferase P1-1 (GSTP1-1) is a phase II detoxifying enzyme and plays a role in resistance to chemotherapeutics. GSTP1-1 may be a prognostic factor in late-stage NHL,[243,244] since survival times were 64 and 25 months for the low and high GSTP1-1 groups, respectively. One strategy to overcome drug resistance would consist of treating relapsed NHL patients concomitantly with chemotherapeutics and GSTP1-1-specific inhibitors.

MAP kinase pathway

The MAP kinase signalling pathway may influence the sensitivity of B-lymphoma cells to chemotherapeutics. The contribution of the MAP kinase pathway and mitochondrial apoptotic pathways was studied in a panel of human B lymphoma cell lines exhibiting varying degrees of drug resistance and Bcl-2/Bax expression.[245] Mitochondrial dysfunction was induced in these cells by the mitochondrial toxicants, carbonyl cyanide *m*-chlorophenylhydrazone (mClCCP) and antimycin A. The drug-resistant lines had higher Bcl-2/Bax expression ratios and were less sensitive to mitochondrial toxicant-induced apoptosis than the sensitive cell lines. Treatment with mitochondrial toxicants led to the activation of the MAP kinase pathway in only the drug-sensitive lines. Specific inhibition of the MAP kinase pathway augmented baseline and mClCCP-induced apoptosis, indicating that differential sensitivity to mitochondrial toxicants in B lymphoma cells involved regulation by MAP kinases.

Tyrosine protein kinases

Oncogenic tyrosine kinases regulate multiple signalling pathways involved in both cell survival and resistance to chemotherapeutics.[246–252] Binding of antigen to the B-cell receptor (BCR) activates phosphorylation of Src family kinases (SFK), which is followed by the activation of MAP kinase, PI3kinase and NFκB pathways[253] resulting in B-cell activation and survival.[254,255]

Over one-third of DLBCL patients tested expressed active SFKs in their tumours and thus may be candidates for treatment with the SFK inhibitor, dasatinib.[256] Dasatinib is dual-kinase inhibitor that is currently approved for use in chronic myelogenous leukemia.[257] In DLBCL cell lines, sensitivity to dasatinib varied by 400-fold, and resistance to dasatinib was associated with the dysregulation downstream of BCR activation.

The anaplastic lymphoma kinase (ALK) is a receptor tyrosine kinase involved in glucocorticoid-resistance in lymphomas.[258] The glucocorticoids, prednisolone and

dexamethasone induce cell-cycle arrest and apoptosis in lymphoid cells and are included in chemotherapeutic regimens for lymphomas.[259,260] Unfortunately, glucocorticoid resistance commonly occurs in lymphomas.[261–264] In about two-thirds of anaplastic large-cell lymphoma (ALCL), a rare type of NHL, a fusion of the nucleophosmin and ALK genes by the t(2;5) chromosomal translocation, gives rise to a hybrid NPM–ALK protein.[265] Dysregulation of ALK caused by fusion to NPM is a causative factor in both ALCL and DLBCL.[266–270] Abnormal activation of ALK is the result of the fusion of the N-terminal NPM partner encoding an oligomerization motif to activate the kinase domain of the ALK protein, which is critical for resistance to glucocorticoids.[271–273]

P53 tumor suppressor gene

P53 mutations are often associated with decreased sensitivity to chemotherapeutics,[274,275] more aggressive clinical course[276] and higher relapse.[16,277–280] Lymphomas with a p53 mutation were more likely to be drug-resistant than those with normal p53 and to have a shorter progression-free survival.[16]

The BH3-only genes, Puma and Noxa, are direct transcriptional targets of p53. The combinatorial action of the p53 target genes, Puma and Noxa, is important for the induction of apoptosis by chemotherapeutics in lymphoma cells.[281] In nontransformed lymphoid cells, the loss of Puma and Noxa induced as much resistance to chemotherapeutics as loss of *p53* itself.

Proteasome

The 26S proteasome complex is a large multisubunit catalytic complex that degrades ubiquitinated proteins.[282] Proteasome inhibition has emerged as a new therapeutic option in lymphoma.[283] The pharmacological proteasome inhibitor (PI), bortezomib (PS-341, Velcade) has shown efficacy against NHL through disrupting the equilibrium between protein biosynthesis and degradation.[282,284–286] Preclinical studies have demonstrated that proteasome inhibition potentiates the activity of other chemotherapeutics.[287,288] However, not all lymphomas are bortezomib-sensitive, and acquired resistance to bortezomib can occur.[284] Although bortezomib has single-agent efficacy in patients with relapsed or refractory MCL,[289–292] about 40–50% of patients develop bortezomib-resistant disease. Bortezomib-resistant lymphoma cell lines exhibited residual proteasome activity in the presence of bortezomib,[293] possibly due to increased expression of the b5, b2 and b1/b5 subunits of the proteasome. Alternative proteolytic systems may take the place of the proteasome leading to resistance to bortezomib.[294–296] Targeting the PI3K/Akt signalling pathway may be a strategy to treat bortezomib-resistant MCL, since the dual PI3K and mTOR inhibitor NVP-BEZ235 overcame bortezomib resistance in MCL cells.

Activation of the endoplasmic reticulum (ER) stress pathway is correlated with resistance to doxorubicin-containing chemotherapy regimens, such as R-CHOP, in DLBCL patients. The 78-kDa glucose-regulated protein (GRP78), also known as immunoglobulin heavy chain binding protein, is an ER stress sensor commonly overexpressed in DLBCL that plays a role doxorubicin- and bortezomib-resistance.[297] Small-interfering RNA silencing of Bip/GRP78 overcame bortezomib resistance.[298]

Epigenetics

Epigenetics plays a critical role in many pathological processes of cancer.[299] Histone deacetylases (HDACs) play a central role cancer epigenetics.[300] HDACs catalyze the removal of acetyl groups from core histones, which leads to the compaction of chromatin and repression of transcription.[301]

HDACs have been implicated in promoting drug resistance in B-cell malignancies.[302,303] Thus, HDAC inhibitors (HDIs) are being investigated as a new therapeutic approach to treat B-cell lymphomas.[304,305]

HDI-mediated inhibition of HDACS results in increased histone acetylation, which can reactivate silenced genes leading to the reversion of drug resistance.[306–310]

Preclinical studies revealed synergistic interactions between proteassome inhibitors (PIs) and HDIs in lymphoma.[311,312] Coadministration of subtoxic concentrations of PIs with HDIs (vorinostat) synergistically increased apoptosis in both GC- and ABC-DLBCL cells, suggesting that a strategy using irreversible PIs to enhance the activity of HDIs might be effective in DLBCL. In other examples, HDIs reversed mTOR (mammalian target of rapamycin) resistance through a phosphatase that antagonized mTORC2 activation,[84] suggesting a combination of HDI and mTOR inhibitors as a strategy for overcoming mTOR resistance in DLBCL. The coadministration of HDIs with rituximab may be a strategy to reverse rituximab resistance in B-cell lymphomas.[313] HDIs enhanced the cytotoxic activity of rituximab by upregulating expression CD20 antigen on lymphoma cells.

MSI instability

MSIs are repetitive DNA sequences. Within MSIs, DNA polymerases are subject to slippage, and misalignments can form between the template and nascent strands. Mismatch repair (MMR) corrects these strand misalignments during DNA replication. MSI is a sign of deficient MMR processes.[314–318] In NHL, MSI may serve as a MMR biomarker that predicts lymphoma response to chemotherapy.[319] MSI was found in 14% of tumours in NHL patients. Response to chemotherapy and outcomes were significantly worse in those NHL patients with MSI tumours.

Stromal influences

Stromal cells are an essential component of the bone marrow microenvironment that influences and supports tumour growth and survival.[320–323] Resistance to chemotherapy can result from cytokines and growth factors released from stromal cells.[320,321] Bone marrow stroma can provide a protective 'sanctuary site' for lymphoma cells during chemotherapy,[324] thus having an impact on the outcome of chemotherapy in DLBCL.[325] Secretion of interleukin-4 and the integrin ligand VCAM-1 from stromal

cells increase survival and rescue B cells from chemotherapy-induced apoptosis.[326,327] Another factor released from bone marrow stromal cells is the lymphoma cell adhesion-induced B cell-activating factor (BAFF) protein, a member of the TNF superfamily of cytokines, which promotes B-cell activation, proliferation and differentiation, thus enhancing B-lymphocyte survival.[328–331] BAFF receptors are expressed on lymphomas originating from diverse subclasses of B-cell lineages.[332] Increased levels of BAFF were present in serum from NHL patients.[332] Small-hairpin RNA depletion of BAFF increased sensitivity of lymphoma cells to chemotherapy and overcame stroma-mediated drug resistance.

Stroma-produced survival signals can influence the expression, conformation and protein–protein interactions of Bax and Bcl-xL, which can then influence the sensitivity of a B-cell lymphoma to chemotherapeutics.[76,333–337] Stroma-mediated activation of CD40 upregulated Bcl-xL protein levels via activation of NFκB. VCAM-1-mediated signals repressed conformational changes in Bax protein and prevented etoposide-induced formation of Bax–Bcl-xL complexes. Stromal upregulation of IL-6 may contribute to the intrinsic chemoresistance commonly found in both primary and metastatic malignancies.[338,339] Additionally, tumour-directed inflammatory responses originating in the stroma that release IL-6 may reduce the efficacy of genotoxic agents.

Lymphocytes home into tissue stromas, which guide the lymphocytes by secreting chemokines and expressing ligands for lymphocyte adhesion molecules. In B-cell lymphomas, the tumour cells retain the trafficking and homing ability of their normal counterparts.[340–343] Lymphoma cells are directed to supporting stroma by chemokine receptors and adhesion molecules, where they receive survival and drug-resistance signals.[344,345] Stromal cells release chemokines, such as CXCL12 and CXCL13, which provide guidance for localizing B-cells within lymph-node compartments.[323,346,347] Lymphocyte homing requires the cooperation between chemokine receptors and adhesion molecules, such as integrins, CD44 and L-selectins.[348] Moreover, accessory cells, including CD68+ macrophages and T cells, in the lymphoma microenvironment can influence the clinical outcome,[349–351] indicating that crosstalk between lymphoma and stromal cells plays an important role in lymphoma progression and chemoresistance.

FL patients frequently are initially sensitive to chemotherapy but then relapse. Highly tumorigenic FL cells exhibiting a cancer stem cell-like phenotype (FL-SC) were found to interact with follicular dendritic cells in a CXCL12/CXCR4-dependent manner to resist chemotherapeutics, indicating an important role for FL-SC and niche cell-signalling in maintaining drug resistance in FL.[352]

Other

Sphingosine kinase. Upregulation of sphingosine kinase 1 (SphK1) frequently occurs in lymphomagenesis. SphK1 is associated with resistance to chemotherapy and radiotherapy.[353,354] SphK1 controls the 'sphingolipid rheostat' by catalyzing the formation of the survival molecule, sphingosine-1-phosphate, at the expense of the pro-apoptotic molecule, ceramide.[355] SphK1 protein and mRNA levels showed increasing expression with increasing clinical grade of NHL.[356]

Geranylation. Inhibition of protein prenylation (geranylgeranylation) can sensitize DLBCL to chemotherapeutics.[357] Prenylation is a post-translational hydrophobic modification of proteins that facilitates the attachment of proteins to membranes. The lipid isoprenoid acts as a lipid anchor, which is essential for proper protein localization and biological function.[358–360] Treatment with simvastatin, an inhibitor of protein farnesylation and geranylgeranylation, sensitized CHOP-resistant DLBCL cells to cytotoxic treatment.[357] Coadministration of protein geranylgeranylation inhibitors and conventional chemotherapeutics thus may be a strategy for treating patients with CHOP refractory DLBCL.

Zinc transporter. Gallium nitrate is a clinically active agent in the treatment of lymphoma.[361–365] Gallium binds to transferrin in the circulation, which targets it to transferrin receptors that are expressed on lymphoma cells.[366–371] Gallium also acts on zinc metabolism pathways.[372] Unfortunately, resistance to gallium can occur, which is caused by the upregulation of metal-responsive transcription factor-1 activity and metallothionein expression.[372] Immunohistochemical staining of lymphomas showed that the metallothionein protein is variably expressed in different lymphomas.

PRDM-1. The positive regulatory domain I (PRDM1) protein regulates the differentiation of mature B lymphocytes to plasma cells.[373,374] The *PRDM1* gene encodes 2 isoforms, PRDM1α and PRDM1β that are regulated by NFκB.[375,376] Those DLBCL cases that expressed PRDM1 displayed more aggressive behaviour and a poorer patient outcome.[377] PRDM1β expression thus might serve as a prognostic marker for drug resistance in some types of DLBCL.

ALDH. The intracellular enzyme retinaldehyde dehydrogenase (ALDH) promotes resistance of MCL to chemotherapeutics.[378–380] ALDH is a cytosolic enzyme required for the biosynthesis of all-*trans*-retinoic acid and is highly expressed by normal hematopoietic and neural stem cells.[381,382] ALDH is expressed in B-cell lymphomas[383,384] and can induce cyclophosphamide resistance in lymphoma cell lines.[385–389]

Summary and conclusions

Both intrinsic genetic alterations as well as chemoprotective microenvironments can play roles in the cellular response of B-cell lymphomas to chemotherapeutics. Given the genetic diversity of B-cell lymphomas and differential antigen expression patterns across lymphoma subtypes, it is unlikely that a single small molecule or antibody-based therapeutic will effectively treat all categories of NHL. Overcoming drug resistance to current chemotherapeutic regimes in B-cell lymphomas will require multitargeted combinatorial therapies to restore apoptotic pathways in

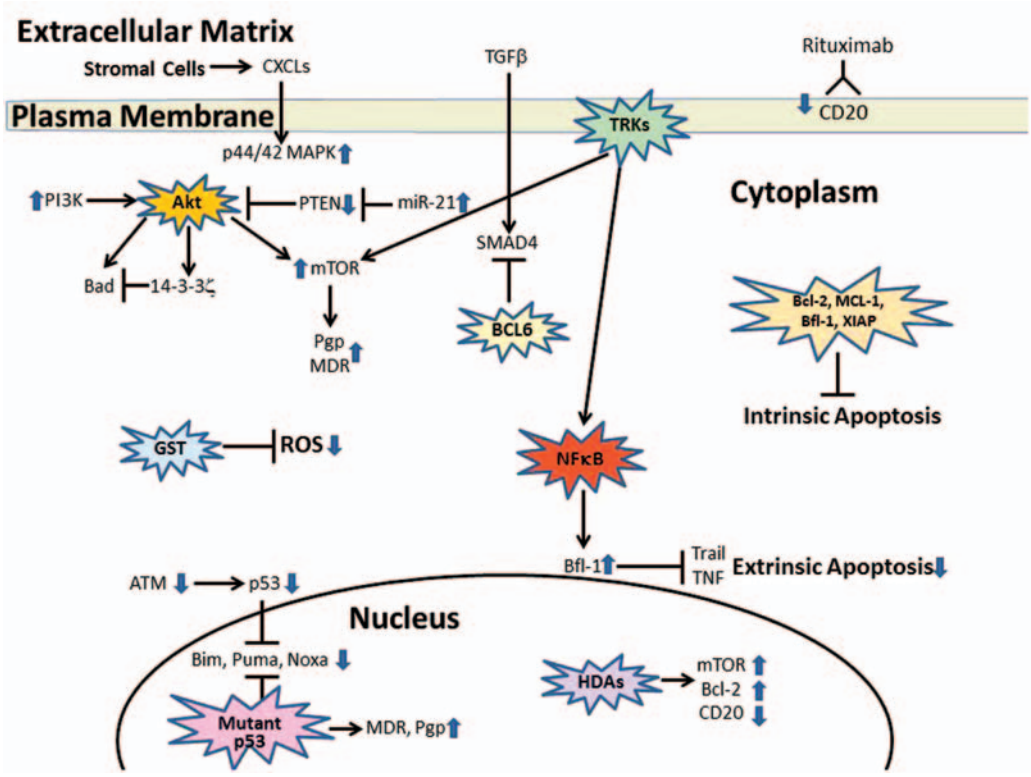

Figure 1 Schematic representation of drug resistance pathways in B-cell lymphomas. PI3K/Akt is frequently activated, which leads to increased mTOR activity stimulating upregulation of multidrug resistance pumps (MDR, Pgp). Akt phosphorylates Bad and 14-3-3ζ, leading to binding and sequestration of the proapoptotic protein Bad and blocking to apoptosis. Upregulation of antiapoptotic proteins (Bcl-2, Mcl-1, XIAP, Bfl-1) can block chemotherapeutic-induced intrinsic apoptosis. The Akt pathway can be activated by upregulation of miR-21, which represses expression of the Akt-negative regulator, PTEN. Activation of tyrosine receptor kinases (TRKs) can induce drug resistance by activating Akt through mTOR. TRKs can also activate NFkB, which upregulates Bfl-1 resulting in blocking of TNF- or Trail-induced extrinsic apoptosis. Upregulation of BCL6 blocks TGFβ-signalling through SMAD4. Glutathione transferases (GSTs) can suppress oxidative stress caused by reactive oxygen species (ROS) that are induced by chemotherapeutics. Histone deacetylases (HDACs) can promote resistance to rituximab combinatorial chemotherapies (R-CHOP) by upregulating mTOR and Bcl-2 and downregulating CD20. Mutation in the p53 gene causes defects in the DNA damage response and upregulation of multidrug resistance pumps (MDR, Pgp). Mutations in Atm can cause deficiencies in the p53-induce DNA damage response, leading to lack of expression of proapoptotic BH3 proteins (Bim, Puma, Noxa) and blocking of intrinsic apoptosis. Downregulation of CD20 through epigenetic silencing can lead to rituximab resistance. (A color version of this figure is available in the online journal)

tumour cells and inhibit prosurvival signalling from the stroma environment.

With the exception of those patients eligible for allogeneic or autologous stem-cell transplantation, combination chemotherapy offers a potentially curative option for a subset of DLBCL patients.[172] However, responses to current combination chemotherapy regimens (e.g. rituximab with cytoxan, hydroxyrubicin, oncovin and prednisone) vary considerably depending on multiple factors, including disease stage and genetic profile, among others. In particular, patients with the ABC-DLBCL subtype, which is NFκB-dependent,[37,390] appear to have a significantly worse prognosis than other subtypes.[391] Collectively, these considerations have motivated the search for more effective combinatorial treatment strategies in DLBCL that are pathway-targeted to specifically target tumour cells without toxicity to nonmalignant cells.

Multitargeted combinatorial experimental therapies composed of new targets and conventional chemotherapeutics may provide more immediate hope for relapsed patients who have failed current chemotherapies. For example, preclinical studies have documented synergistic interactions between PIs, such as bortezomib and HDAC inhibitors in diverse malignant cell types.[311,392,393] Targeting CD40 with dacetuzumab enhanced the antitumor activity of rituximab (CD20) in cell line and xenograft NHL models.[394] In MCL, a sequence-dependent synergistic effect was observed with PIs in combination with cytarabine.[395] Tipifarnib and bortezomib combination was well-tolerated and produced clinical responses in refractory acute leukemias.[396] Multilevel inhibition of the PI3K/Akt/mTOR and cdc2/cdk1 cell-cycle pathways may be more effective in treating DLBCL patients that present with overactive Akt and cdc2/cdk1.[397]

Thus, understanding genotype-response relationships in NHL will be important for the effective use of new targeted therapies in the clinic. Responsiveness to multitargeted therapies will be predicted based on molecular markers to predefine patients who will most likely benefit from these targeted therapies. For instance, 'BH3 profiling' can identify those cells that are sensitive to the Bcl-2 antagonist ABT-737.[398] Determining the activity of the NFκB pathway in DLBCL tumour biopsies by GEP can predict responsiveness to the IκB kinase inhibitor PS1145.[105] Future approaches to

NHL treatment will employ molecular signatures identified through GEP to provide prognostic information and to identify therapeutic targets in patients who relapse or those presenting with high risk disease to guide clinicians in designing a personalized approach to combinatorial molecular therapies.

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REFERENCES

1. Armitage JO, Weisenburger DD. New approach to classifying non-Hodgkin's lymphomas: clinical features of the major histologic subtypes. Non-Hodgkin's Lymphoma Classification Project. *J Clin Oncol* 1998;**16**:2780–95
2. Coiffier B. Monoclonal antibody as therapy for malignant lymphomas. *CR Biol* 2006;**329**:241–54
3. Klein U, Dalla-Favera R. Germinal centres: role in B-cell physiology and malignancy. *Nat Rev Immunol* 2008;**8**:22–33
4. Fisher RI. CHOP chemotherapy as standard therapy for treatment of patients with diffuse histiocytic lymphoma. *Important Adv Oncol* 1990;217–25
5. Czuczman MS, Leonard JP, Williams ME. Recent advances in the treatment of mantle cell lymphoma: a post-ASH 2009 discussion. *Clin Adv Hematol Oncol* 2010;**8**:A1–14; quiz A15
6. Friedberg JW, Fisher RI. Diffuse large B-cell lymphoma. *Hematol Oncol Clin North Am* 2008;**22**:941–52, ix
7. Velasquez WS. Prognostic factors in aggressive lymphoma. *J Clin Oncol* 1991;**9**:1320–1
8. Velasquez WS. Prognostic factors in intermediate high grade lymphoma. *Cancer Treat Res* 1993;**66**:37–52
9. Fisher RI, Gaynor ER, Dahlberg S, Oken MM, Grogan TM, Mize EM, Glick JH, Coltman CA Jr, Miller TP. Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma. *N Engl J Med* 1993;**328**:1002–6
10. Multani P, White CA, Grillo-Lopez A. Non-Hodgkin's lymphoma: review of conventional treatments. *Curr Pharm Biotechnol* 2001;**2**:279–91
11. Sonneveld P, de Ridder M, van der Lelie H, Nieuwenhuis K, Schouten H, Mulder A, van Reijswoud I, Hop W, Lowenberg B. Comparison of doxorubicin and mitoxantrone in the treatment of elderly patients with advanced diffuse non-Hodgkin's lymphoma using CHOP versus CNOP chemotherapy. *J Clin Oncol* 1995;**13**:2530–9
12. Coffey J, Hodgson DC, Gospodarowicz MK. Therapy of non-Hodgkin's lymphoma. *Eur J Nucl Med Mol Imaging* 2003;**30**(Suppl 1): S28–36
13. Swerdlow AJ. Epidemiology of Hodgkin's disease and non-Hodgkin's lymphoma. *Eur J Nucl Med Mol Imaging* 2003;**30**(Suppl 1): S3–12
14. Theodossiou C, Schwarzenberger P. Non-Hodgkin's lymphomas. *Clin Obstet Gynecol* 2002;**45**:820–9
15. Navaratnam S, Williams GJ, Rubinger M, Pettigrew NM, Mowat MR, Begleiter A, Johnston JB. Expression of p53 predicts treatment failure in aggressive non-Hodgkin's lymphomas. *Leuk Lymph* 1998;**29**:139–44
16. Wilson WH, Teruya-Feldstein J, Fest T, Harris C, Steinberg SM, Jaffe ES, Raffeld M. Relationship of p53, bcl-2, and tumor proliferation to clinical drug resistance in non-Hodgkin's lymphomas. *Blood* 1997;**89**:601–9
17. Holen KD, Saltz LB. New therapies, new directions: advances in the systemic treatment of metastatic colorectal cancer. *Lancet Oncol* 2001;**2**:290–7
18. Ansell SM, Armitage J. Non-Hodgkin lymphoma: diagnosis and treatment. *Mayo Clin Proc* 2005;**80**:1087–97
19. O'Leary HM, Savage KJ. Novel therapies in peripheral T-cell lymphomas. *Curr Hematol Malig Rep* 2008;**3**:213–20
20. Cheung MC, Haynes AE, Meyer RM, Stevens A, Imrie KR. Rituximab in lymphoma: a systematic review and consensus practice guideline from Cancer Care Ontario. *Cancer Treat Rev* 2007;**33**:161–76
21. Ng AK. Diffuse large B-cell lymphoma. *Semin Radiat Oncol* 2007;**17**:169–75
22. Prichard M, Harris T, Williams ME, Densmore JJ. Treatment strategies for relapsed and refractory aggressive non-Hodgkin's lymphoma. *Expert Opin Pharmacother* **10**:983–95
23. Horning SJ. Natural history of and therapy for the indolent non-Hodgkin's lymphomas. *Semin Oncol* 1993;**20**:75–88
24. Meusers P, Hense J, Brittinger G. Mantle cell lymphoma: diagnostic criteria, clinical aspects and therapeutic problems. *Leukemia* 1997;**11**(Suppl 2): S60–4
25. Schmidt C, Dreyling M. Therapy of mantle cell lymphoma: current standards and future strategies. *Hematol Oncol Clin North Am* **22**:953–63, ix
26. Harris NL, Jaffe ES, Stein H, Banks PM, Chan JK, Cleary ML, Delsol G, De Wolf-Peeters C, Falini B, Gatter KC, Grogan TM, Isaacson PG, Knowles DM, Mason DY, Muller-Hermelink H, Pileri SA, Piris MA, Ralfkiaer E, Warnke RA. A revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. *Blood* 1994;**84**:1361–92
27. Campo E, Raffeld M, Jaffe ES. Mantle-cell lymphoma. *Semin Hematol* 1999;**36**:115–27
28. Philip T, Guglielmi C, Hagenbeek A, Somers R, Van der Lelie H, Bron D, Sonneveld P, Gisselbrecht C, Cahn JY, Harousseau JL, Coiffier B, Biron P, Mandelli F, Chauvin F. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. *N Engl J Med* 1995;**333**:1540–5
29. Niehans GA, Jaszcz W, Brunetto V, Perri RT, Gajl-Peczalska K, Wick MR, Tsuruo T, Bloomfield CD. Immunohistochemical identification of P-glycoprotein in previously untreated, diffuse large cell and immunoblastic lymphomas. *Cancer Res* 1992;**52**:3768–75
30. Bates SE, Wilson WH, Fojo AT, Alvarez M, Zhan Z, Regis J, Robey R, Hose C, Monks A, Kang YK, Chabner B. Clinical reversal of multidrug resistance. *Stem Cell* 1996;**14**:56–63
31. Webb M, Brun M, McNiven M, Le Couteur D, Craft P. MDR1 and MRP expression in chronic B-cell lymphoproliferative disorders. *Br J Haematol* 1998;**102**:710–7
32. Houldsworth J, Petlakh M, Olshen AB, Chaganti RS. Pathway activation in large B-cell non-Hodgkin lymphoma cell lines by doxorubicin reveals prognostic markers of in vivo response. *Leuk Lymphoma* 2008;**49**:2170–80
33. Alizadeh AA, Eisen MB, Davis RE, Ma C, Lossos IS, Rosenwald A, Boldrick JC, Sabet H, Tran T, Yu X, Powell JI, Yang L, Marti GE, Moore T, Hudson J Jr, Lu L, Lewis DB, Tibshirani R, Sherlock G, Chan WC, Greiner TC, Weisenburger DD, Armitage JO, Warnke R, Levy R, Wilson W, Grever MR, Byrd JC, Botstein D, Brown PO, Staudt LM. Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. *Nature* 2000;**403**:503–11
34. Rosenwald A, Wright G, Chan WC, Connors JM, Campo E, Fisher RI, Gascoyne RD, Muller-Hermelink HK, Smeland EB, Giltnane JM, Hurt EM, Zhao H, Averett L, Yang L, Wilson WH, Jaffe ES, Simon R, Klausner RD, Powell J, Duffey PL, Longo DL, Greiner TC, Weisenburger DD, Sanger WG, Dave BJ, Lynch JC, Vose J, Armitage JO, Montserrat E, Lopez-Guillermo A, Grogan TM, Miller TP, LeBlanc M, Ott G, Kvaloy S, Delabie J, Holte H, Krajci P, Stokke T, Staudt LM. The use of molecular profiling to predict survival after chemotherapy for diffuse large-B-cell lymphoma. *N Engl J Med* 2002;**346**:1937–47
35. Wright G, Tan B, Rosenwald A, Hurt EH, Wiestner A, Staudt LM. A gene expression-based method to diagnose clinically distinct subgroups of diffuse large B cell lymphoma. *Proc Natl Acad Sci USA* 2003;**100**:9991–6
36. Bea S, Zettl A, Wright G, Salaverria I, Jehn P, Moreno V, Burek C, Ott G, Puig X, Yang L, Lopez-Guillermo A, Chan WC, Greiner TC, Weisenburger DD, Armitage JO, Gascoyne RD, Connors JM,

Grogan TM, Braziel R, Fisher RI, Smeland EB, Kvaloy S, Holte H, Delabie J, Simon R, Powell J, Wilson WH, Jaffe ES, Montserrat E, Muller-Hermelink HK, Staudt LM, Campo E, Rosenwald A. Diffuse large B-cell lymphoma subgroups have distinct genetic profiles that influence tumor biology and improve gene-expression-based survival prediction. *Blood* 2005;**106**:3183–90

37. Davis RE, Brown KD, Siebenlist U, Staudt LM. Constitutive nuclear factor kappaB activity is required for survival of activated B cell-like diffuse large B cell lymphoma cells. *J Exp Med* 2001;**194**:1861–74
38. Monti S, Savage KJ, Kutok JL, Feuerhake F, Kurtin P, Mihm M, Wu B, Pasqualucci L, Neuberg D, Aguiar RC, Cin PD, Ladd C, Pinkus GS, Salles G, Harris NL, Dalla-Faver R, Habermann TM, Aster JC, Golub TR, Shipp MA. Molecular profiling of diffuse large B-cell lymphoma identifies robust subtypes including one characterized by host inflammatory response. *Blood* 2005;**105**:1851–61
39. Leonard JP, Schattner EJ, Coleman M. Biology and management of mantle cell lymphoma. *Curr Opin Oncol* 2001;**13**:342–7
40. Vandenberghe E, De Wolf-Peeters C, Vaughan Hudson G, Hudson BV, Pittaluga S, Anderson L, Linch DC. The clinical outcome of 65 cases of mantle cell lymphoma initially treated with non-intensive therapy by the British National Lymphoma Investigation Group. *Br J Haematol* 1997;**99**:842–7
41. Royo C, Salaverria I, Hartmann EM, Rosenwald A, Campo E, Bea S. The complex landscape of genetic alterations in mantle cell lymphoma. *Semin Cancer Biol* 2011;**21**:322–34
42. Jares P, Colomer D, Campo E. Genetic and molecular pathogenesis of mantle cell lymphoma: perspectives for new targeted therapeutics. *Nat Rev Cancer* 2007;**7**:750–62
43. Smith MR. Mantle cell lymphoma: advances in biology and therapy. *Curr Opin Hematol* 2008;**15**:415–21
44. Martinez N, Camacho FI, Algara P, Rodriguez A, Dopazo A, Ruiz-Ballesteros E, Martin P, Martinez-Climent JA, Garcia-Conde J, Menarguez J, Solano F, Mollejo M, Piris MA. The molecular signature of mantle cell lymphoma reveals multiple signals favoring cell survival. *Cancer Res* 2003;**63**:8226–32
45. Fu L, Lin-Lee YC, Pham LV, Tamayo A, Yoshimura L, Ford RJ. Constitutive NF-kappaB and NFAT activation leads to stimulation of the BLyS survival pathway in aggressive B-cell lymphomas. *Blood* 2006;**107**:4540–8
46. Pham LV, Tamayo AT, Yoshimura LC, Lo P, Ford RJ. Inhibition of constitutive NF-kappa B activation in mantle cell lymphoma B cells leads to induction of cell cycle arrest and apoptosis. *J Immunol* 2003;**171**:88–95
47. Shishodia S, Amin HM, Lai R, Aggarwal BB. Curcumin (diferuloylmethane) inhibits constitutive NF-kappaB activation, induces G1/S arrest, suppresses proliferation, and induces apoptosis in mantle cell lymphoma. *Biochem Pharmacol* 2005;**70**:700–13
48. Tucker CA, Kapanen AI, Chikh G, Hoffman BG, Kyle AH, Wilson IM, Masin D, Gascoyne RD, Bally M, Klasa RJ. Silencing Bcl-2 in models of mantle cell lymphoma is associated with decreases in cyclin D1, nuclear factor-kappaB, p53, bax, and p27 levels. *Mol Cancer Ther* 2008;**7**:749–58
49. Thieblemont C, Nasser V, Felman P, Leroy K, Gazzo S, Callet-Bauchu E, Loriod B, Granjeaud S, Gaulard P, Haioun C, Traverse-Glehen A, Baseggio L, Bertucci F, Birnbaum D, Magrangeas F, Minvielle S, Avet-Loiseau H, Salles G, Coiffier B, Berger F, Houlgatte R. Small lymphocytic lymphoma, marginal zone B-cell lymphoma, and mantle cell lymphoma exhibit distinct gene-expression profiles allowing molecular diagnosis. *Blood* 2004;**103**:2727–37
50. Bennaceur-Griscelli A, Bosq J, Koscielny S, Lefrere F, Turhan A, Brousse N, Hermine O, Ribrag V. High level of glutathione-S-transferase pi expression in mantle cell lymphomas. *Clin Cancer Res* 2004;**10**:3029–34
51. Rizzatti EG, Falcao RP, Panepucci RA, Proto-Siqueira R, Anselmo-Lima WT, Okamoto OK, Zago MA. Gene expression profiling of mantle cell lymphoma cells reveals aberrant expression of genes from the PI3K-AKT, WNT and TGFbeta signalling pathways. *Br J Haematol* 2005;**130**:516–26
52. Rizzatti EG, Mora-Jensen H, Weniger MA, Gibellini F, Lee E, Daibata M, Lai R, Wiestner A. Noxa mediates bortezomib induced apoptosis in both sensitive and intrinsically resistant mantle cell lymphoma cells and this effect is independent of constitutive activity of the AKT and NF-kappaB pathways. *Leuk Lymphoma* 2008;**49**:798–808
53. Ghielmini M, Zucca E. How I treat mantle cell lymphoma. *Blood* 2009;**114**:1469–76
54. Alessi DR, James SR, Downes CP, Holmes AB, Gaffney PR, Reese CB, Cohen P. Characterization of a 3-phosphoinositide-dependent protein kinase which phosphorylates and activates protein kinase Balpha. *Curr Biol* 1997;**7**:261–9
55. Kawauchi K, Ogasawara T, Yasuyama M, Otsuka K, Yamada O. The PI3K/Akt pathway as a target in the treatment of hematologic malignancies. *Anticancer Agents Med Chem* 2009;**9**:550–9
56. Manning BD, Cantley LC. AKT/PKB signaling: navigating downstream. *Cell* 2007;**129**:1261–74
57. Stokoe D, Stephens LR, Copeland T, Gaffney PR, Reese CB, Painter GF, Holmes AB, McCormick F, Hawkins PT. Dual role of phosphatidylinositol-3,4,5-trisphosphate in the activation of protein kinase B. *Science* 1997;**277**:567–70
58. Jung HJ, Chen Z, McCarty N. Stem-like tumor cells confer drug resistant properties to mantle cell lymphoma. *Leuk Lymphoma* 2011;**52**:1066–79
59. Baohua Y, Xiaoyan Z, Tiecheng Z, Tao Q, Daren S. Mutations of the PIK3CA gene in diffuse large B cell lymphoma. *Diagn Mol Pathol* 2008;**17**:159–65
60. Bonavida B. Rituximab-induced inhibition of antiapoptotic cell survival pathways: implications in chemo/immunoresistance, rituximab unresponsiveness, prognostic and novel therapeutic interventions. *Oncogene* 2007;**26**:3629–36
61. Fridberg M, Servin A, Anagnostaki L, Linderoth J, Berglund M, Soderberg O, Enblad G, Rosen A, Mustelin T, Jerkeman M, Persson JL, Wingren AG. Protein expression and cellular localization in two prognostic subgroups of diffuse large B-cell lymphoma: higher expression of ZAP70 and PKC-beta II in the non-germinal center group and poor survival in patients deficient in nuclear PTEN. *Leuk Lymphoma* 2007;**48**:2221–32
62. Hasselblom S, Hansson U, Olsson M, Toren L, Bergstrom A, Nilsson-Ehle H, Andersson PO. High immunohistochemical expression of p-AKT predicts inferior survival in patients with diffuse large B-cell lymphoma treated with immunochemotherapy. *Br J Haematol* 2010;**149**:560–8
63. Renne C, Willenbrock K, Martin-Subero JI, Hinsch N, Doring C, Tiacci E, Klapper W, Moller P, Kuppers R, Hansmann ML, Siebert R, Brauninger A. High expression of several tyrosine kinases and activation of the PI3K/AKT pathway in mediastinal large B cell lymphoma reveals further similarities to Hodgkin lymphoma. *Leukemia* 2007;**21**:780–7
64. Uddin S, Bu R, Ahmed M, Hussain AR, Ajarim D, Al-Dayel F, Bavi P, Al-kuraya KS. Leptin receptor expression and its association with PI3K/AKT signaling pathway in diffuse large B-cell lymphoma. *Leuk Lymphoma* 2010;**51**:1305–14
65. Uddin S, Hussain AR, Ahmed M, Al-Dayel F, Bu R, Bavi P, Al-Kuraya KS. Inhibition of c-MET is a potential therapeutic strategy for treatment of diffuse large B-cell lymphoma. *Lab Invest* 2010;**90**:1346–56
66. Nakao A, Afrakhte M, Moren A, Nakayama T, Christian JL, Heuchel R, Itoh S, Kawabata M, Heldin NE, Heldin CH, ten Dijke P. Identification of Smad7, a TGFbeta-inducible antagonist of TGF-beta signalling. *Nature* 1997;**389**:631–5
67. Imamura T, Takase M, Nishihara A, Oeda E, Hanai J, Kawabata M, Miyazono K. Smad6 inhibits signalling by the TGF-beta superfamily. *Nature* 1997;**389**:622–6
68. Wendel HG, De Stanchina E, Fridman JS, Malina A, Ray S, Kogan S, Cordon-Cardo C, Pelletier J, Lowe SW. Survival signalling by Akt and eIF4E in oncogenesis and cancer therapy. *Nature* 2004;**428**:332–7
69. Hess G, Herbrecht R, Romaguera J, Verhoef G, Crump M, Gisselbrecht C, Laurell A, Offner F, Strahs A, Berkenblit A, Hanushevsky O, Clancy J, Hewes B, Moore L, Coiffier B. Phase III study to evaluate temsirolimus compared with investigator's choice therapy for the treatment of relapsed or refractory mantle cell lymphoma. *J Clin Oncol* 2009;**27**:3822–9
70. Shi Y, Massague J. Mechanisms of TGF-beta signaling from cell membrane to the nucleus. *Cell* 2003;**113**:685–700

71. Chen G, Ghosh P, Osawa H, Sasaki CY, Rezanka L, Yang J, O'Farrell TJ, Longo DL. Resistance to TGF-beta 1 correlates with aberrant expression of TGF-beta receptor II in human B-cell lymphoma cell lines. *Blood* 2007;**109**:5301–7
72. Wang D, Long J, Dai F, Liang M, Feng XH, Lin X. BCL6 represses Smad signaling in transforming growth factor-beta resistance. *Cancer Res* 2008;**68**:783–9
73. Wendel HG, Malina A, Zhao Z, Zender L, Kogan SC, Cordon-Cardo C, Pelletier J, Lowe SW. Determinants of sensitivity and resistance to rapamycin-chemotherapy drug combinations in vivo. *Cancer Res* 2006;**66**:7639–46
74. Allard D, Figg N, Bennett MR, Littlewood TD. Akt regulates the survival of vascular smooth muscle cells via inhibition of FoxO3a and GSK3. *J Biol Chem* 2008;**283**:19739–47
75. Datta SR, Brunet A, Greenberg ME. Cellular survival: a play in three Akts. *Genes Dev* 1999;**13**:2905–27
76. del Peso L, Gonzalez-Garcia M, Page C, Herrera R, Nunez G. Interleukin-3-induced phosphorylation of BAD through the protein kinase Akt. *Science* 1997;**278**:687–9
77. Goldman EH, Chen L, Fu H. Activation of apoptosis signal-regulating kinase 1 by reactive oxygen species through dephosphorylation at serine 967 and 14-3-3 dissociation. *J Biol Chem* 2004;**279**:10442–9
78. Jope RS, Johnson GV. The glamour and gloom of glycogen synthase kinase-3. *Trends Biochem Sci* 2004;**29**:95–102
79. Kim I, Shu CW, Xu W, Shiau CW, Grant D, Vasile S, Cosford ND, Reed JC. Chemical biology investigation of cell death pathways activated by endoplasmic reticulum stress reveals cytoprotective modulators of ASK1. *J Biol Chem* 2009;**284**:1593–603
80. Yan L, Lavin VA, Moser LR, Cui Q, Kanies C, Yang E. PP2A regulates the pro-apoptotic activity of FOXO1. *J Biol Chem* 2008;**283**:7411–20
81. Suzuki E, Umezawa K, Bonavida B. Rituximab inhibits the constitutively activated PI3K-Akt pathway in B-NHL cell lines: involvement in chemosensitization to drug-induced apoptosis. *Oncogene* 2007;**26**:6184–93
82. Maxwell SA, Cherry EM, Bayless KJ. Akt, 14-3-3zeta, and vimentin mediate a drug-resistant invasive phenotype in diffuse large B-cell lymphoma. *Leuk Lymphoma* 2011;**52**:849–64
83. Maxwell SA, Li Z, Jaye D, Ballard S, Ferrell J, Fu H. 14-3-3zeta mediates resistance of diffuse large B cell lymphoma to an anthracycline-based chemotherapeutic regimen. *J Biol Chem* 2009;**284**:22379–89
84. Gupta M, Ansell SM, Novak AJ, Kumar S, Kaufmann SH, Witzig TE. Inhibition of histone deacetylase overcomes rapamycin-mediated resistance in diffuse large B-cell lymphoma by inhibiting Akt signaling through mTORC2. *Blood* 2009;**114**:2926–35
85. Smith SM, van Besien K, Karrison T, Dancey J, McLaughlin P, Younes A, Smith S, Stiff P, Lester E, Modi S, Doyle LA, Vokes EE, Pro B. Temsirolimus has activity in non-mantle cell non-Hodgkin's lymphoma subtypes: The University of Chicago phase II consortium. *J Clin Oncol* 2010;**28**:4740–6
86. Witzig TE, Reeder CB, LaPlant BR, Gupta M, Johnston PB, Micallef IN, Porrata LF, Ansell SM, Colgan JP, Jacobsen ED, Ghobrial IM, Habermann TM. A phase II trial of the oral mTOR inhibitor everolimus in relapsed aggressive lymphoma. *Leukemia* 2011;**25**:341–7
87. Schatz JH. Targeting the PI3K/AKT/mTOR pathway in non-Hodgkin's lymphoma: results, biology, and development strategies. *Curr Oncol Rep* 2011;**13**:398–406
88. Krammer PH. CD95's deadly mission in the immune system. *Nature* 2000;**407**:789–95
89. Plumas J, Jacob MC, Chaperot L, Molens JP, Sotto JJ, Bensa JC. Tumor B cells from non-Hodgkin's lymphoma are resistant to CD95 (Fas/Apo-1)-mediated apoptosis. *Blood* 1998;**91**:2875–85
90. Thomas RK, Kallenborn A, Wickenhauser C, Schultze JL, Draube A, Vockerodt M, Re D, Diehl V, Wolf J. Constitutive expression of c-FLIP in Hodgkin and Reed-Sternberg cells. *Am J Pathol* 2002;**160**:1521–8
91. Kelley RF, Totpal K, Lindstrom SH, Mathieu M, Billeci K, Deforge L, Pai R, Hymowitz SG, Ashkenazi A. Receptor-selective mutants of apoptosis-inducing ligand 2/tumor necrosis factor-related apoptosis-inducing ligand reveal a greater contribution of death receptor (DR) 5 than DR4 to apoptosis signaling. *J Biol Chem* 2005;**280**:2205–12
92. Scaffidi C, Kirchhoff S, Krammer PH, Peter ME. Apoptosis signaling in lymphocytes. *Curr Opin Immunol* 1999;**11**:277–85
93. Siegel RM, Chan FK, Chun HJ, Lenardo MJ. The multifaceted role of Fas signaling in immune cell homeostasis and autoimmunity. *Nat Immunol* 2000;**1**:469–74
94. Ashkenazi A, Pai RC, Fong S, Leung S, Lawrence DA, Marsters SA, Blackie C, Chang L, McMurtrey AE, Hebert A, DeForge L, Koumenis IL, Lewis D, Harris L, Bussiere J, Koeppen H, Shahrokh Z, Schwall RH. Safety and antitumor activity of recombinant soluble Apo2 ligand. *J Clin Invest* 1999;**104**:155–62
95. Walczak H, Miller RE, Ariail K, Gliniak B, Griffith TS, Kubin M, Chin W, Jones J, Woodward A, Le T, Smith C, Smolak P, Goodwin RG, Rauch CT, Schuh JC, Lynch DH. Tumoricidal activity of tumor necrosis factor-related apoptosis-inducing ligand in vivo. *Nat Med* 1999;**5**:157–63
96. Wiley SR, Schooley K, Smolak PJ, Din WS, Huang CP, Nicholl JK, Sutherland GR, Smith TD, Rauch C, Smith CA, Goodwin RG. Identification and characterization of a new member of the TNF family that induces apoptosis. *Immunity* 1995;**3**:673–82
97. Cillessen SA, Meijer CJ, Ossenkoppele GJ, Castricum KC, Westra AH, Niesten P, Muris JJ, Nijdam HF, van der Hem KG, Flens M, Hooijberg E, Oudejans JJ. Human soluble TRAIL/Apo2L induces apoptosis in a subpopulation of chemotherapy refractory nodal diffuse large B-cell lymphomas, determined by a highly sensitive in vitro apoptosis assay. *Br J Haematol* 2006;**134**:283–93
98. Bodmer JL, Holler N, Reynard S, Vinciguerra P, Schneider P, Juo P, Blenis J, Tschopp J. TRAIL receptor-2 signals apoptosis through FADD and caspase-8. *Nat Cell Biol* 2000;**2**:241–3
99. Pitti RM, Marsters SA, Ruppert S, Donahue CJ, Moore A, Ashkenazi A. Induction of apoptosis by Apo-2 ligand, a new member of the tumor necrosis factor cytokine family. *J Biol Chem* 1996;**271**:12687–90
100. Brien G, Trescol-Biemont MC, Bonnefoy-Berard N. Downregulation of Bfl-1 protein expression sensitizes malignant B cells to apoptosis. *Oncogene* 2007;**26**:5828–32
101. Grumont RJ, Rourke IJ, Gerondakis S. Rel-dependent induction of A1 transcription is required to protect B cells from antigen receptor ligation-induced apoptosis. *Genes Dev* 1999;**13**:400–11
102. Wang CY, Guttridge DC, Mayo MW, Baldwin AS Jr. NF-kappaB induces expression of the Bcl-2 homologue A1/Bfl-1 to preferentially suppress chemotherapy-induced apoptosis. *Mol Cell Biol* 1999;**19**:5923–9
103. Zong WX, Edelstein LC, Chen C, Bash J, Gelinas C. The prosurvival Bcl-2 homolog Bfl-1/A1 is a direct transcriptional target of NF-kappaB that blocks TNFalpha-induced apoptosis. *Genes Dev* 1999;**13**:382–7
104. Werner AB, de Vries E, Tait SW, Bontjer I, Borst J. Bcl-2 family member Bfl-1/A1 sequesters truncated bid to inhibit is collaboration with pro-apoptotic Bak or Bax. *J Biol Chem* 2002;**277**:22781–8
105. Lam LT, Davis RE, Pierce J, Hepperle M, Xu Y, Hottelet M, Nong Y, Wen D, Adams J, Dang L, Staudt LM. Small molecule inhibitors of IkappaB kinase are selectively toxic for subgroups of diffuse large B-cell lymphoma defined by gene expression profiling. *Clin Cancer Res* 2005;**11**:28–40
106. Danial NN, Korsmeyer SJ. Cell death: critical control points. *Cell* 2004;**116**:205–19
107. van Delft MF, Huang DC. How the Bcl-2 family of proteins interact to regulate apoptosis. *Cell Res* 2006;**16**:203–13
108. Puthalakath H, Strasser A. Keeping killers on a tight leash: transcriptional and post-translational control of the pro-apoptotic activity of BH3-only proteins. *Cell Death Differ* 2002;**9**:505–12
109. Sun Y, Orrenius S, Pervaiz S, Fadeel B. Plasma membrane sequestration of apoptotic protease-activating factor-1 in human B-lymphoma cells: a novel mechanism of chemoresistance. *Blood* 2005;**105**:4070–7
110. Johnstone RW, Ruefli AA, Lowe SW. Apoptosis: a link between cancer genetics and chemotherapy. *Cell* 2002;**108**:153–64
111. Reed JC. Bcl-2 and the regulation of programmed cell death. *J Cell Biol* 1994;**124**:1–6
112. Shangary S, Johnson DE. Peptides derived from BH3 domains of Bcl-2 family members: a comparative analysis of inhibition of Bcl-2, Bcl-x(L)

and Bax oligomerization, induction of cytochrome c release, and activation of cell death. *Biochemistry* 2002;**41**:9485–95
113. Wang JL, Liu D, Zhang ZJ, Shan S, Han X, Srinivasula SM, Croce CM, Alnemri ES, Huang Z. Structure-based discovery of an organic compound that binds Bcl-2 protein and induces apoptosis of tumor cells. *Proc Natl Acad Sci USA* 2000;**97**:7124–9
114. Yang J, Liu X, Bhalla K, Kim CN, Ibrado AM, Cai J, Peng TI, Jones DP, Wang X. Prevention of apoptosis by Bcl-2: release of cytochrome c from mitochondria blocked. *Science* 1997;**275**:1129–32
115. Kluck RM, Bossy-Wetzel E, Green DR, Newmeyer DD. The release of cytochrome c from mitochondria: a primary site for Bcl-2 regulation of apoptosis. *Science* 1997;**275**:1132–6
116. Yang E, Korsmeyer SJ. Molecular thanatopsis: a discourse on the BCL2 family and cell death. *Blood* 1996;**88**:386–401
117. Yunis JJ, Frizzera G, Oken MM, McKenna J, Theologides A, Arnesen M. Multiple recurrent genomic defects in follicular lymphoma. A possible model for cancer. *N Engl J Med* 1987;**316**:79–84
118. Gascoyne RD, Adomat SA, Krajewski S, Krajewska M, Horsman DE, Tolcher AW, O'Reilly SE, Hoskins P, Coldman AJ, Reed JC, Connors JM. Prognostic significance of Bcl-2 protein expression and Bcl-2 gene rearrangement in diffuse aggressive non-Hodgkin's lymphoma. *Blood* 1997;**90**:244–51
119. Hermine O, Haioun C, Lepage E, d'Agay MF, Briere J, Lavignac C, Fillet G, Salles G, Marolleau JP, Diebold J, Reyas F, Gaulard P. Prognostic significance of bcl-2 protein expression in aggressive non-Hodgkin's lymphoma. Groupe d'Etude des Lymphomes de l'Adulte (GELA). *Blood* 1996;**87**:265–72
120. Hill ME, MacLennan KA, Cunningham DC, Vaughan Hudson B, Burke M, Clarke P, Di Stefano F, Anderson L, Vaughan Hudson G, Mason D, Selby P, Linch DC. Prognostic significance of BCL-2 expression and bcl-2 major breakpoint region rearrangement in diffuse large cell non-Hodgkin's lymphoma: a British National Lymphoma Investigation Study. *Blood* 1996;**88**:1046–51
121. Sanchez E, Chacon I, Plaza MM, Munoz E, Cruz MA, Martinez B, Lopez L, Martinez-Montero JC, Orradre JL, Saez AI, Garcia JF, Piris MA. Clinical outcome in diffuse large B-cell lymphoma is dependent on the relationship between different cell-cycle regulator proteins. *J Clin Oncol* 1998;**16**:1931–9
122. Chanan-Khan A. Bcl-2 antisense therapy in B-cell malignancies. *Blood Rev* 2005;**19**:213–21
123. Waters JS, Webb A, Cunningham D, Clarke PA, Raynaud F, di Stefano F, Cotter FE. Phase I clinical and pharmacokinetic study of bcl-2 antisense oligonucleotide therapy in patients with non-Hodgkin's lymphoma. *J Clin Oncol* 2000;**18**:1812–23
124. Kitada S, Takayama S, De Riel K, Tanaka S, Reed JC. Reversal of chemoresistance of lymphoma cells by antisense-mediated reduction of bcl-2 gene expression. *Antisense Res Dev* 1994;**4**:71–9
125. Pro B, Leber B, Smith M, Fayad L, Romaguera J, Hagemeister F, Rodriguez A, McLaughlin P, Samaniego F, Zwiebel J, Lopez A, Kwak L, Younes A. Phase II multicenter study of oblimersen sodium, a Bcl-2 antisense oligonucleotide, in combination with rituximab in patients with recurrent B-cell non-Hodgkin lymphoma. *Br J Haematol* 2008;**143**:355–60
126. Rathmell JC, Thompson CB. The central effectors of cell death in the immune system. *Annu Rev Immunol* 1999;**17**:781–828
127. Duckett CS, Nava VE, Gedrich RW, Clem RJ, Van Dongen JL, Gilfillan MC, Shiels H, Hardwick JM, Thompson CB. A conserved family of cellular genes related to the baculovirus iap gene and encoding apoptosis inhibitors. *EMBO J* 1996;**15**:2685–94
128. Liston P, Roy N, Tamai K, Lefebvre C, Baird S, Cherton-Horvat G, Farahani R, McLean M, Ikeda JE, MacKenzie A, Korneluk RG. Suppression of apoptosis in mammalian cells by NAIP and a related family of IAP genes. *Nature* 1996;**379**:349–53
129. Muris JJ, Cillessen SA, Vos W, van Houdt IS, Kummer JA, van Krieken JH, Jiwa NM, Jansen PM, Kluin-Nelemans HC, Ossenkoppele GJ, Gundy C, Meijer CJ, Oudejans JJ. Immunohistochemical profiling of caspase signaling pathways predicts clinical response to chemotherapy in primary nodal diffuse large B-cell lymphomas. *Blood* 2005;**105**:2916–23
130. Cillessen SA, Hess CJ, Hooijberg E, Castricum KC, Kortman P, Denkers F, Vos W, van de Wiel MA, Schuurhuis GJ, Ossenkoppele GJ, Meijer CJ, Oudejans JJ. Inhibition of the intrinsic apoptosis pathway downstream of caspase-9 activation causes chemotherapy resistance in diffuse large B-cell lymphoma. *Clin Cancer Res* 2007;**13**:7012–21
131. Cillessen SA, Reed JC, Welsh K, Pinilla C, Houghten R, Hooijberg E, Deurhof J, Castricum KC, Kortman P, Hess CJ, Ossenkoppele GJ, Meijer CJ, Oudejans JJ. Small-molecule XIAP antagonist restores caspase-9 mediated apoptosis in XIAP-positive diffuse large B-cell lymphoma cells. *Blood* 2008;**111**:369–75
132. Savitsky K, Bar-Shira A, Gilad S, Rotman G, Ziv Y, Vanagaite L, Tagle DA, Smith S, Uziel T, Sfez S, Ashkenazi M, Pecker I, Frydman M, Harnik R, Patanjali SR, Simmons A, Clines GA, Sartiel A, Gatti RA, Chessa L, Sanal O, Lavin MF, Jaspers NG, Taylor AM, Arlett CF, Miki T, Weissman SM, Lovett M, Collins FS, Shiloh Y. A single ataxia telangiectasia gene with a product similar to PI-3 kinase. *Science* 1995;**268**:1749–53
133. Korz C, Pscherer A, Benner A, Mertens D, Schaffner C, Leupolt E, Dohner H, Stilgenbauer S, Lichter P. Evidence for distinct pathomechanisms in B-cell chronic lymphocytic leukemia and mantle cell lymphoma by quantitative expression analysis of cell cycle and apoptosis-associated genes. *Blood* 2002;**99**:4554–61
134. Pusapati RV, Rounbehler RJ, Hong S, Powers JT, Yan M, Kiguchi K, McArthur MJ, Wong PK, Johnson DG. ATM promotes apoptosis and suppresses tumorigenesis in response to Myc. *Proc Natl Acad Sci USA* 2006;**103**:1446–51
135. Shreeram S, Hee WK, Demidov ON, Kek C, Yamaguchi H, Fornace AJ Jr, Anderson CW, Appella E, Bulavin DV. Regulation of ATM/p53-dependent suppression of myc-induced lymphomas by Wip1 phosphatase. *J Exp Med* 2006;**203**:2793–9
136. Reimann M, Loddenkemper C, Rudolph C, Schildhauer I, Teichmann B, Stein H, Schlegelberger B, Dorken B, Schmitt CA. The Myc-evoked DNA damage response accounts for treatment resistance in primary lymphomas in vivo. *Blood* 2007;**110**:2996–3004
137. Baldwin AS. Control of oncogenesis and cancer therapy resistance by the transcription factor NF-kappaB. *J Clin Invest* 2001;**107**:241–6
138. Jost PJ, Ruland J. Aberrant NF-kappaB signaling in lymphoma: mechanisms, consequences, and therapeutic implications. *Blood* 2007;**109**:2700–7
139. Hayden MS, Ghosh S. Signaling to NF-kappaB. *Genes Dev* 2004;**18**:2195–224
140. Karin M. Nuclear factor-kappaB in cancer development and progression. *Nature* 2006;**441**:431–6
141. Kim HJ, Hawke N, Baldwin AS. NF-kappaB and IKK as therapeutic targets in cancer. *Cell Death Differ* 2006;**13**:738–47
142. Luo JL, Kamata H, Karin M. IKK/NF-kappaB signaling: balancing life and death – a new approach to cancer therapy. *J Clin Invest* 2005;**115**:2625–32
143. Jazirehi AR, Vega MI, Chatterjee D, Goodglick L, Bonavida B. Inhibition of the Raf-MEK1/2-ERK1/2 signaling pathway, Bcl-xL down-regulation, and chemosensitization of non-Hodgkin's lymphoma B cells by Rituximab. *Cancer Res* 2004;**64**:7117–26
144. Thomas RK, Sos ML, Zander T, Mani O, Popov A, Berenbrinker D, Smola-Hess S, Schultze JL, Wolf J. Inhibition of nuclear translocation of nuclear factor-kappaB despite lack of functional IkappaBalpha protein overcomes multiple defects in apoptosis signaling in human B-cell malignancies. *Clin Cancer Res* 2005;**11**:8186–94
145. Bai H, Wei J, Deng C, Yang X, Wang C, Xu R. MicroRNA-21 regulates the sensitivity of diffuse large B-cell lymphoma cells to the CHOP chemotherapy regimen. *Int J Hematol* 2013;**97**:223–31
146. Hayashita Y, Osada H, Tatematsu Y, Yamada H, Yanagisawa K, Tomida S, Yatabe Y, Kawahara K, Sekido Y, Takahashi T. A polycistronic microRNA cluster, miR-17-92, is overexpressed in human lung cancers and enhances cell proliferation. *Cancer Res* 2005;**65**:9628–32
147. He L, Thomson JM, Hemann MT, Hernando-Monge E, Mu D, Goodson S, Powers S, Cordon-Cardo C, Lowe SW, Hannon GJ, Hammond SM. A microRNA polycistron as a potential human oncogene. *Nature* 2005;**435**:828–33

148. Ota A, Tagawa H, Karnan S, Tsuzuki S, Karpas A, Kira S, Yoshida Y, Seto M. Identification and characterization of a novel gene, C13orf25, as a target for 13q31-q32 amplification in malignant lymphoma. *Cancer Res* 2004;**64**:3087–95
149. Rao E, Jiang C, Ji M, Huang X, Iqbal J, Lenz G, Wright G, Staudt LM, Zhao Y, McKeithan TW, Chan WC, Fu K. The miRNA-17 approximately 92 cluster mediates chemoresistance and enhances tumor growth in mantle cell lymphoma via PI3K/AKT pathway activation. *Leukemia* 2012;**26**:1064–72
150. Hayashi H, Abdollah S, Qiu Y, Cai J, Xu YY, Grinnell BW, Richardson MA, Topper JN, Gimbrone MA Jr, Wrana JL, Falb D. The MAD-related protein Smad7 associates with the TGFbeta receptor and functions as an antagonist of TGFbeta signaling. *Cell* 1997;**89**:1165–73
151. Tome ME, Baker AF, Powis G, Payne CM, Briehl MM. Catalase-overexpressing thymocytes are resistant to glucocorticoid-induced apoptosis and exhibit increased net tumor growth. *Cancer Res* 2001;**61**:2766–73
152. Tome ME, Briehl MM. Thymocytes selected for resistance to hydrogen peroxide show altered antioxidant enzyme profiles and resistance to dexamethasone-induced apoptosis. *Cell Death Differ* 2001;**8**:953–61
153. Wilkinson ST, Johnson DB, Tardif HL, Tome ME, Briehl MM. Increased cytochrome c correlates with poor survival in aggressive lymphoma. *Oncol Lett* 2010;**1**:227–30
154. Tome ME, Johnson DB, Rimsza LM, Roberts RA, Grogan TM, Miller TP, Oberley LW, Briehl MM. A redox signature score identifies diffuse large B-cell lymphoma patients with a poor prognosis. *Blood* 2005;**106**:3594–601
155. Tome ME, Lutz NW, Briehl MM. Overexpression of catalase or Bcl-2 alters glucose and energy metabolism concomitant with dexamethasone resistance. *Biochim Biophys Acta* 2004;**1693**:57–72
156. Certo M, Del Gaizo Moore V, Nishino M, Wei G, Korsmeyer S, Armstrong SA, Letai A. Mitochondria primed by death signals determine cellular addiction to antiapoptotic BCL-2 family members. *Cancer Cell* 2006;**9**:351–65
157. Willis SN, Fletcher JI, Kaufmann T, van Delft MF, Chen L, Czabotar PE, Ierino H, Lee EF, Fairlie WD, Bouillet P, Strasser A, Kluck RM, Adams JM, Huang DC. Apoptosis initiated when BH3 ligands engage multiple Bcl-2 homologs, not Bax or Bak. *Science* 2007;**315**:856–9
158. Tome ME, Frye JB, Coyle DL, Jacobson EL, Samulitis BK, Dvorak K, Dorr RT, Briehl MM. Lymphoma cells with increased anti-oxidant defenses acquire chemoresistance. *Experimental Ther Med* 2012;**3**:845–52
159. Gatenby RA, Gillies RJ. Why do cancers have high aerobic glycolysis? *Nat Rev Cancer* 2004;**4**:8919
160. Raghunand N, He X, van Sluis R, Mahoney B, Baggett B, Taylor CW, Paine-Murrieta G, Roe D, Bhujwalla ZM, Gillies RJ. Enhancement of chemotherapy by manipulation of tumour pH. *Br J Cancer* 1999;**80**:1005–11
161. De Milito A, Fais S. Tumor acidity, chemoresistance and proton pump inhibitors. *Future Oncol* 2005;**1**:779–86
162. Gatenby RA, Gawlinski ET. The glycolytic phenotype in carcinogenesis and tumor invasion: insights through mathematical models. *Cancer Res* 2003;**63**:3847–54
163. Sennoune SR, Luo D, Martinez-Zaguilan R. Plasmalemmal vacuolar-type H+-ATPase in cancer biology. *Cell Biochem Biophys* 2004;**40**:185–206
164. De Milito A, Iessi E, Logozzi M, Lozupone F, Spada M, Marino ML, Federici C, Perdicchio M, Matarrese P, Lugini L, Nilsson A, Fais S. Proton pump inhibitors induce apoptosis of human B-cell tumors through a caspase-independent mechanism involving reactive oxygen species. *Cancer Res* 2007;**67**:5408–17
165. O'Brien ML, Tew KD. Glutathione and related enzymes in multidrug resistance. *Eur J Cancer A* 1996;**32**:967–78
166. Cowan KH, Batist G, Tulpule A, Sinha BK, Myers CE. Similar biochemical changes associated with multidrug resistance in human breast cancer cells and carcinogen-induced resistance to xenobiotics in rats. *Proc Natl Acad Sci USA* 1986;**83**:9328–32
167. McGown AT, Fox BW. A proposed mechanism of resistance to cyclophosphamide and phosphoramide mustard in a Yoshida cell line in vitro. *Cancer Chemother Pharmacol* 1986;**17**:223–6
168. Robson CN, Lewis AD, Wolf CR, Hayes JD, Hall A, Proctor SJ, Harris AL, Hickson ID. Reduced levels of drug-induced DNA cross-linking in nitrogen mustard-resistant Chinese hamster ovary cells expressing elevated glutathione S-transferase activity. *Cancer Res* 1987;**47**:6022–7
169. Schisselbauer JC, Silber R, Papadopoulos E, Abrams K, LaCreta FP, Tew KD. Characterization of glutathione S-transferase expression in lymphocytes from chronic lymphocytic leukemia patients. *Cancer Res* 1990;**50**:3562–8
170. Teicher BA, Holden SA, Kelley MJ, Shea TC, Cucchi CA, Rosowsky A, Henner WD, Frei E. III. Characterization of a human squamous carcinoma cell line resistant to cis-diamminedichloroplatinum(II). *Cancer Res* 1987;**47**:388–93
171. Tew KD. Glutathione-associated enzymes in anticancer drug resistance. *Cancer Res* 1994;**54**:4313–20
172. Coiffier B, Lepage E, Briere J, Herbrecht R, Tilly H, Bouabdallah R, Morel P, Van Den Neste E, Salles G, Gaulard P, Reyes F, Lederlin P, Gisselbrecht C. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. *N Engl J Med* 2002;**346**:235–42
173. Sehn LH, Donaldson J, Chhanabhai M, Fitzgerald C, Gill K, Klasa R, MacPherson N, O'Reilly S, Spinelli JJ, Sutherland J, Wilson KS, Gascoyne RD, Connors JM. Introduction of combined CHOP plus rituximab therapy dramatically improved outcome of diffuse large B-cell lymphoma in British Columbia. *J Clin Oncol* 2005;**23**:5027–33
174. Coiffier B, Haioun C, Ketterer N, Engert A, Tilly H, Ma D, Johnson P, Lister A, Feuring-Buske M, Radford JA, Capdeville R, Diehl V, Reyes F. Rituximab (anti-CD20 monoclonal antibody) for the treatment of patients with relapsing or refractory aggressive lymphoma: a multicenter phase II study. *Blood* 1998;**92**:1927–32
175. Hess G, Flohr T, Kolbe K, Bonn S, Schuler M, Derigs HG, Huber C. Effect of rituximab on the long-term outcome after high-dose therapy for relapsed B-cell non-Hodgkin's lymphoma. *Ann Hematol* 2006;**85**:769–79
176. Hiddemann W, Kneba M, Dreyling M, Schmitz N, Lengfelder E, Schmits R, Reiser M, Metzner B, Harder H, Hegewisch-Becker S, Fischer T, Kropff M, Reis HE, Freund M, Wormann B, Fuchs R, Planker M, Schimke J, Eimermacher H, Trumper L, Aldaoud A, Parwaresch R, Unterhalt M. Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. *Blood* 2005;**106**:3725–32
177. Marcus R, Imrie K, Belch A, Cunningham D, Flores E, Catalano J, Solal-Celigny P, Offner F, Walewski J, Raposo J, Jack A, Smith P. CVP chemotherapy plus rituximab compared with CVP as first-line treatment for advanced follicular lymphoma. *Blood* 2005;**105**:1417–23
178. Pfreundschuh M, Trumper L, Osterborg A, Pettengell R, Trneny M, Imrie K, Ma D, Gill D, Walewski J, Zinzani PL, Stahel R, Kvaloy S, Shpilberg O, Jaeger U, Hansen M, Lehtinen T, Lopez-Guillermo A, Corrado C, Scheliga A, Milpied N, Mendila M, Rashford M, Kuhnt E, Loeffler M. CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MInT) Group. *Lancet Oncol* 2006;**7**:379–91
179. Vellenga E, van Putten WL, van't Veer MB, Zijlstra JM, Fibbe WE, van Oers MH, Verdonck LF, Wijermans PW, van Imhoff GW, Lugtenburg PJ, Huijgens PC. Rituximab improves the treatment results of DHAP-VIM-DHAP and ASCT in relapsed/progressive aggressive CD20+ NHL: a prospective randomized HOVON trial. *Blood* 2008;**111**:537–43
180. Maloney DG, Liles TM, Czerwinski DK, Waldichuk C, Rosenberg J, Grillo-Lopez A, Levy R. Phase I clinical trial using escalating single-dose infusion of chimeric anti-CD20 monoclonal antibody (IDEC-

C2B8) in patients with recurrent B-cell lymphoma. *Blood* 1994;**84**:2457–66
181. Press OW, Appelbaum F, Ledbetter JA, Martin PJ, Zarling J, Kidd P, Thomas ED. Monoclonal antibody 1F5 (anti-CD20) serotherapy of human B cell lymphomas. *Blood* 1987;**69**:584–91
182. Einfeld DA, Brown JP, Valentine MA, Clark EA, Ledbetter JA. Molecular cloning of the human B cell CD20 receptor predicts a hydrophobic protein with multiple transmembrane domains. *EMBO J* 1988;**7**:711–17
183. Kimby E. Tolerability and safety of rituximab (MabThera). *Cancer Treat Rev* 2005;**31**:456–73
184. Smith MR. Rituximab (monoclonal anti-CD20 antibody): mechanisms of action and resistance. *Oncogene* 2003;**22**:7359–68
185. Martin P, Furman RR, Coleman M, Leonard JP. Phase I to III trials of anti-B cell therapy in non-Hodgkin's lymphoma. *Clin Cancer Res* 2007;**13**:5636s–42s
186. Coiffier B. Rituximab therapy in malignant lymphoma. *Oncogene* 2007;**26**:3603–13
187. Colombat P, Salles G, Brousse N, Eftekhari P, Soubeyran P, Delwail V, Deconinck E, Haioun C, Foussard C, Sebban C, Stamatoullas A, Milpied N, Boue F, Taillan B, Lederlin P, Najman A, Thieblemont C, Montestruc F, Mathieu-Boue A, Benzohra A, Solal-Celigny P. Rituximab (anti-CD20 monoclonal antibody) as single first-line therapy for patients with follicular lymphoma with a low tumor burden: clinical and molecular evaluation. *Blood* 2001;**97**:101–6
188. Ghielmini M, Schmitz SF, Cogliatti SB, Pichert G, Hummerjohann J, Waltzer U, Fey MF, Betticher DC, Martinelli G, Peccatori F, Hess U, Zucca E, Stupp R, Kovacsovics T, Helg C, Lohri A, Bargetzi M, Vorobiof D, Cerny T. Prolonged treatment with rituximab in patients with follicular lymphoma significantly increases event-free survival and response duration compared with the standard weekly x 4 schedule. *Blood* 2004;**103**:4416–23
189. Hainsworth JD, Litchy S, Burris HAIII, Scullin DC Jr, Corso SW, Yardley DA, Morrissey L, Greco FA. Rituximab as first-line and maintenance therapy for patients with indolent non-hodgkin's lymphoma. *J Clin Oncol* 2002;**20**:4261–7
190. Hainsworth JD, Litchy S, Shaffer DW, Lackey VL, Grimaldi M, Greco FA. Maximizing therapeutic benefit of rituximab: maintenance therapy versus re-treatment at progression in patients with indolent non-Hodgkin's lymphoma – a randomized phase II trial of the Minnie Pearl Cancer Research Network. *J Clin Oncol* 2005;**23**:1088–95
191. Lemieux B, Bouafia F, Thieblemont C, Hequet O, Arnaud P, Tartas S, Traulle C, Salles G, Coiffier B. Second treatment with rituximab in B-cell non-Hodgkin's lymphoma: efficacy and toxicity on 41 patients treated at CHU-Lyon Sud. *Hematol J* 2004;**5**:467–71
192. McLaughlin P, Grillo-Lopez AJ, Link BK, Levy R, Czuczman MS, Williams ME, Heyman MR, Bence-Bruckler I, White CA, Cabanillas F, Jain V, Ho AD, Lister J, Wey K, Shen D, Dallaire BK. Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: half of patients respond to a four-dose treatment program. *J Clin Oncol* 1998;**16**:2825–33
193. Maloney DG. Immunotherapy for non-Hodgkin's lymphoma: monoclonal antibodies and vaccines. *J Clin Oncol* 2005;**23**:6421–8
194. Clynes RA, Towers TL, Presta LG, Ravetch JV. Inhibitory Fc receptors modulate in vivo cytoxicity against tumor targets. *Nat Med* 2000;**6**:443–6
195. Kennedy GA, Tey SK, Cobcroft R, Marlton P, Cull G, Grimmett K, Thomson D, Gill D. Incidence and nature of CD20-negative relapses following rituximab therapy in aggressive B-cell non-Hodgkin's lymphoma: a retrospective review. *Br J Haematol* 2002;**119**:412–6
196. Daniels I, Abulayha AM, Thomson BJ, Haynes AP. Caspase-independent killing of Burkitt lymphoma cell lines by rituximab. *Apoptosis* 2006;**11**:1013–23
197. Hofmeister JK, Cooney D, Coggeshall KM. Clustered CD20 induced apoptosis: src-family kinase, the proximal regulator of tyrosine phosphorylation, calcium influx, and caspase 3-dependent apoptosis. *Blood Cells Mol Dis* 2000;**26**:133–43
198. Popoff IJ, Savage JA, Blake J, Johnson P, Deans JP. The association between CD20 and Src-family Tyrosine kinases requires an additional factor. *Mol Immunol* 1998;**35**:207–14
199. Shan D, Ledbetter JA, Press OW. Apoptosis of malignant human B cells by ligation of CD20 with monoclonal antibodies. *Blood* 1998;**91**:1644–52
200. Shan D, Ledbetter JA, Press OW. Signaling events involved in anti-CD20-induced apoptosis of malignant human B cells. *Cancer Immunol Immunother* 2000;**48**:673–83
201. Walshe CA, Beers SA, French RR, Chan CH, Johnson PW, Packham GK, Glennie MJ, Cragg MS. Induction of cytosolic calcium flux by CD20 is dependent upon B Cell antigen receptor signaling. *J Biol Chem* 2008;**283**:16971–84
202. Olejniczak SH, Hernandez-Ilizaliturri FJ, Clements JL, Czuczman MS. Acquired resistance to rituximab is associated with chemotherapy resistance resulting from decreased Bax and Bak expression. *Clin Cancer Res* 2008;**14**:1550–60
203. Davidson B, Konstantinovsky S, Nielsen S, Dong HP, Berner A, Vyberg M, Reich R. Altered expression of metastasis-associated and regulatory molecules in effusions from breast cancer patients: a novel model for tumor progression. *Clin Cancer Res* 2004;**10**:7335–46
204. Gabison EE, Hoang-Xuan T, Mauviel A, Menashi S. EMMPRIN/CD147, an MMP modulator in cancer, development and tissue repair. *Biochimie* 2005;**87**:361–8
205. Misra S, Ghatak S, Zoltan-Jones A, Toole BP. Regulation of multidrug resistance in cancer cells by hyaluronan. *J Biol Chem* 2003;**278**:25285–8
206. Reimers N, Zafrakas K, Assmann V, Egen C, Riethdorf L, Riethdorf S, Berger J, Ebel S, Janicke F, Sauter G, Pantel K. Expression of extracellular matrix metalloproteases inducer on micrometastatic and primary mammary carcinoma cells. *Clin Cancer Res* 2004;**10**:3422–8
207. Zou W, Yang H, Hou X, Zhang W, Chen B, Xin X. Inhibition of CD147 gene expression via RNA interference reduces tumor cell invasion, tumorigenicity and increases chemosensitivity to paclitaxel in HO-8910pm cells. *Cancer Lett* 2007;**248**:211–8
208. Zucker S, Hymowitz M, Rollo EE, Mann R, Conner CE, Cao J, Foda HD, Tompkins DC, Toole BP. Tumorigenic potential of extracellular matrix metalloproteinase inducer. *Am J Pathol* 2001;**158**:1921–8
209. Illemann M, Bird N, Majeed A, Sehested M, Laerum OD, Lund LR, Dano K, Nielsen BS. MMP-9 is differentially expressed in primary human colorectal adenocarcinomas and their metastases. *Mol Cancer Res* 2006;**4**:293–302
210. Jia L, Wei W, Cao J, Xu H, Miao X, Zhang J. Silencing CD147 inhibits tumor progression and increases chemosensitivity in murine lymphoid neoplasm P388D1 cells. *Ann Hematol* 2009;**88**:753–60
211. Simon SM, Schindler M. Cell biological mechanisms of multidrug resistance in tumors. *Proc Natl Acad Sci USA* 1994;**91**:3497–504
212. Gottesman MM, Pastan I. Biochemistry of multidrug resistance mediated by the multidrug transporter. *Annu Rev Biochem* 1993;**62**:385–427
213. Kerb R, Hoffmeyer S, Brinkmann U. ABC drug transporters: hereditary polymorphisms and pharmacological impact in MDR1, MRP1 and MRP2. *Pharmacogenomics* 2001;**2**:51–64
214. Litman T, Druley TE, Stein WD, Bates SE. From MDR to MXR: new understanding of multidrug resistance systems, their properties and clinical significance. *Cell Mol Life Sci* 2001;**58**:931–59
215. Szakacs G, Paterson JK, Ludwig JA, Booth-Genthe C, Gottesman MM. Targeting multidrug resistance in cancer. *Nat Rev Drug Discov* 2006;**5**:219–34
216. Kang YK, Zhan Z, Regis J, Alvarez M, Robey R, Meadows B, Dickstein B, Lee JS, Otsuki T, Stetler-Stevenson M, Jaffe ES, Solomon D, Wilson WH, Fojo A, Bate SE. Expression of mdr-1 in refractory lymphoma: quantitation by polymerase chain reaction and validation of the assay. *Blood* 1995;**86**:1515–24
217. Pileri SA, Sabattini E, Falini B, Tazzari PL, Gherlinzoni F, Michieli MG, Damiani D, Zucchini L, Gobbi M, Tsuruo T, Baccarani M. Immunohistochemical detection of the multidrug transport protein P170 in human normal tissues and malignant lymphomas. *Histopathology* 1991;**19**:131–40
218. Ohsawa M, Ikura Y, Fukushima H, Shirai N, Sugama Y, Suekane T, Hirayama M, Hino M, Ueda M. Immunohistochemical expression of

multidrug resistance proteins as a predictor of poor response to chemotherapy and prognosis in patients with nodal diffuse large B-cell lymphoma. *Oncology* 2005;**68**:422–31
219. Moscow JA, Fairchild CR, Madden MJ, Ransom DT, Wieand HS, O'Brien EE, Poplack DG, Cossman J, Myers CE, Cowan KH. Expression of anionic glutathione-*S*-transferase and P-glycoprotein genes in human tissues and tumors. *Cancer Res* 1989;**49**:1422–8
220. Miller TP, Grogan TM, Dalton WS, Spier CM, Scheper RJ, Salmon SE. P-glycoprotein expression in malignant lymphoma and reversal of clinical drug resistance with chemotherapy plus high-dose verapamil. *J Clin Oncol* 1991;**9**:17–24
221. Wilson WH, Bates SE, Fojo A, Bryant G, Zhan Z, Regis J, Wittes RE, Jaffe ES, Steinberg SM, Herdt J. Controlled trial of dexverapamil, a modulator of multidrug resistance, in lymphomas refractory to EPOCH chemotherapy. *J Clin Oncol* 1995;**13**:1995–2004
222. Yahanda AM, Alder KM, Fisher GA, Brophy NA, Halsey J, Hardy RI, Gosland MP, Lum BL, Sikic BI. Phase I trial of etoposide with cyclosporine as a modulator of multidrug resistance. *J Clin Oncol* 1992;**10**:1624–34
223. Rodriguez C, Commes T, Robert J, Rossi JF. Expression of P-glycoprotein and anionic glutathione S-transferase genes in non-Hodgkin's lymphoma. *Leuk Res* 1993;**17**:149–56
224. Finnegan MC, Royds J, Goepel JR, Lorigan P, Hancock BW, Goyns MH. MDR-1 expression in non-Hodgkin's lymphomas is unrelated to treatment intensity or response to therapy. *Leuk Lymphoma* 1995;**18**:297–302
225. Zhan Z, Sandor VA, Gamelin E, Regis J, Dickstein B, Wilson W, Fojo AT, Bates SE. Expression of the multidrug resistance-associated protein gene in refractory lymphoma: quantitation by a validated polymerase chain reaction assay. *Blood* 1997;**89**:3795–800
226. Goldstein LJ, Galski H, Fojo A, Willingham M, Lai SL, Gazdar A, Pirker R, Green A, Crist W, Brodeur GM, Lieber M, Cossman J, Michael M, Gottesman MM, Pastan I. Expression of a multidrug resistance gene in human cancers. *J Natl Cancer Inst* 1989;**81**:116–24
227. Holzmayer TA, Hilsenbeck S, Von Hoff DD, Roninson IB. Clinical correlates of MDR1 (P-glycoprotein) gene expression in ovarian and small-cell lung carcinomas. *J Natl Cancer Inst* 1992;**84**:1486–91
228. Garcia MG, Alaniz LD, Russo RIC, Alvarez E, Hajos SE. PI3K/Akt inhibition modulates multidrug resistance and activates NF-kappaB in murine lymphoma cell lines. *Leuk Res* 2009;**33**:288–96
229. Kim JE, Singh RR, Cho-Vega JH, Drakos E, Davuluri Y, Khokhar FA, Fayad L, Medeiros LJ, Vega F. Sonic hedgehog signaling proteins and ATP-binding cassette G2 are aberrantly expressed in diffuse large B-cell lymphoma. *Mod Pathol* 2009;**22**:1312–20
230. Singh RR, Kunkalla K, Qu C, Schlette E, Neelapu SS, Samaniego F, Vega F. ABCG2 is a direct transcriptional target of hedgehog signaling and involved in stroma-induced drug tolerance in diffuse large B-cell lymphoma. *Oncogene* 2011;**30**:4874–86
231. Scheper RJ, Broxterman HJ, Scheffer GL, Kaaijk P, Dalton WS, van Heijningen TH, van Kalken CK, Slovak ML, de Vries EG, van der Valk P, Meijer CJLM, Pinedo HM. Ov erexpression of a M(r) 110,000 vesicular protein in non-P-glycoprotein-mediated multidrug resistance. *Cancer Res* 1993;**53**:1475–9
232. Scheffer GL, Wijngaard PL, Flens MJ, Izquierdo MA, Slovak ML, Pinedo HM, Meijer CJ, Clevers HC, Scheper RJ. The drug resistance-related protein LRP is the human major vault protein. *Nat Med* 1995;**1**:578–82
233. Kedersha NL, Rome LH. Isolation and characterization of a novel ribonucleoprotein particle: large structures contain a single species of small RNA. *J Cell Biol* 1986;**103**:699–709
234. Izquierdo MA, Shoemaker RH, Flens MJ, Scheffer GL, Wu L, Prather TR, Scheper RJ. Overlapping phenotypes of multidrug resistance among panels of human cancer-cell lines. *Int J Cancer* 1996;**65**:230–7
235. Kitazono M, Sumizawa T, Takebayashi Y, Chen ZS, Furukawa T, Nagayama S, Tani A, Takao S, Aikou T, Akiyama S. Multidrug resistance and the lung resistance-related protein in human colon carcinoma SW-620 cells. *J Natl Cancer Inst* 1999;**91**:1647–53
236. Filipits M, Jaeger U, Simonitsch I, Chizzali-Bonfadin C, Heinzl H, Pirker R. Clinical relevance of the lung resistance protein in diffuse large B-cell lymphomas. *Clin Cancer Res* 2000;**6**:3417–23
237. Wolf CR, Macpherson JS, Smyth JF. Evidence for the metabolism of mitozantrone by microsomal glutathione transferases and 3-methylcholanthrene-inducible glucuronosyl transferases. *Biochem Pharmacol* **35**:1577–81
238. Batist G, Tulpule A, Sinha BK, Katki AG, Myers CE, Cowan KH. Overexpression of a novel anionic glutathione transferase in multidrug-resistant human breast cancer cells. *J Biol Chem* 1986;**261**:15544–9
239. Gupta V, Singh SV, Ahmad H, Medh RD, Awasthi YC. Glutathione and glutathione S-transferases in a human plasma cell line resistant to melphalan. *Biochem Pharmacol* 1989;**38**:1993–2000
240. Bolton MG, Colvin OM, Hilton J. Specificity of isozymes of murine hepatic glutathione S-transferase for the conjugation of glutathione with L-phenylalanine mustard. *Cancer Res* 1991;**51**:2410–5
241. Lewis AD, Hickson ID, Robson CN, Harris AL, Hayes JD, Griffiths SA, Manson MM, Hall AE, Moss JE, Wolf CR. Amplification and increased expression of alpha class glutathione S-transferase-encoding genes associated with resistance to nitrogen mustards. *Proc Natl Acad Sci USA* 1988;**85**:8511–5
242. Puchalski RB, Fahl WE. Expression of recombinant glutathione S-transferase pi, Ya, or Yb1 confers resistance to alkylating agents. *Proc Natl Acad Sci USA* 1990;**87**:2443–7
243. Ribrag V, Koscielny S, Carpiuc I, Cebotaru C, Vande Walle H, Talbot M, Fenaux P, Bosq J. Prognostic value of GST-pi expression in diffuse large B-cell lymphomas. *Leukemia* 2003;**17**:972–7
244. Katahira T, Takayama T, Miyanishi K, Hayashi T, Ikeda T, Takahashi Y, Takimoto R, Matsunaga T, Kato J, Niitsu Y. Plasma glutathione *S*-transferase P1-1 as a prognostic factor in patients with advanced non-Hodgkin's lymphoma (stages III and IV). *Clin Cancer Res* 2004;**10**:7934–40
245. O'Brien KA, Muscarella DE, Bloom SE. Differential induction of apoptosis and MAP kinase signaling by mitochondrial toxicants in drug-sensitive compared to drug-resistant B-lineage lymphoid cell lines. *Toxicol Appl Pharmacol* 2001;**174**:245–56
246. Greenland C, Touriol C, Chevillard G, Morris SW, Bai R, Duyster J, Delsol G, Allouche M. Expression of the oncogenic NPM-ALK chimeric protein in human lymphoid T-cells inhibits drug-induced, but not Fas-induced apoptosis. *Oncogene* 2001;**20**:7386–97
247. Liu Q, Schwaller J, Kutok J, Cain D, Aster JC, Williams IR, Gilliland DG. Signal transduction and transforming properties of the TEL-TRKC fusions associated with t(12;15)(p13;q25) in congenital fibrosarcoma and acute myelogenous leukemia. *EMBO J* 2000;**19**:1827–38
248. Masumoto N, Nakano S, Fujishima H, Kohno K, Niho Y. v-src induces cisplatin resistance by increasing the repair of cisplatin-DNA interstrand cross-links in human gallbladder adenocarcinoma cells. *Int J Cancer* 1999;**80**:731–7
249. Pietras RJ, Fendly BM, Chazin VR, Pegram MD, Howell SB, Slamon DJ. Antibody to HER-2/neu receptor blocks DNA repair after cisplatin in human breast and ovarian cancer cells. *Oncogene* 1994;**9**:1829–38
250. Raitano AB, Whang YE, Sawyers CL. Signal transduction by wild-type and leukemogenic Abl proteins. *Biochim Biophys Acta* 1997;**1333**:F201–16
251. Sattler M, Salgia R. Activation of hematopoietic growth factor signal transduction pathways by the human oncogene BCR/ABL. *Cytokine Growth Factor Rev* 1997;**8**:63–79
252. Zou X, Calame K. Signaling pathways activated by oncogenic forms of Abl tyrosine kinase. *J Biol Chem* 1999;**274**:18141–4
253. Thomas SM, Brugge JS. Cellular functions regulated by Src family kinases. *Annu Rev Cell Dev Biol* 1997;**13**:513–609
254. Dal Porto JM, Gauld SB, Merrell KT, Mills D, Pugh-Bernard AE, Cambier J. B cell antigen receptor signaling 101. *Mol Immunol* 2004;**41**:599–613
255. Monroe JG. ITAM-mediated tonic signalling through pre-BCR and BCR complexes. *Nat Rev Immunol* 2006;**6**:283–94
256. Hollmann CA, Tzankov A, Martinez-Marignac VL, Baker K, Grygorczyk C, Grygorczyk R, Foulkes W, Nadeau J, Dirnhofer S,

Aloyz R. Therapeutic implications of Src independent calcium mobilization in diffuse large B-cell lymphoma. *Leuk Res* 2010;**34**:585–93
257. Brave M, Goodman V, Kaminskas E, Farrell A, Timmer W, Pope S, Harapanhalli R, Saber H, Morse D, Bullock J, Men A, Noory C, Ramchandani R, Kenna L, Booth B, Gobburu J, Jiang X, Sridhara R, Justice R, Pazdur R. Sprycel for chronic myeloid leukemia and Philadelphia chromosome-positive acute lymphoblastic leukemia resistant to or intolerant of imatinib mesylate. *Clin Cancer Res* 2008;**14**:352–9
258. Morris SW, Naeve C, Mathew P, James PL, Kirstein MN, Cui X, Witte DP. ALK, the chromosome 2 gene locus altered by the t(2;5) in non-Hodgkin's lymphoma, encodes a novel neural receptor tyrosine kinase that is highly related to leukocyte tyrosine kinase (LTK). *Oncogene* 1997;**14**:2175–88
259. Greenstein S, Ghias K, Krett NL, Rosen ST. Mechanisms of glucocorticoid-mediated apoptosis in hematological malignancies. *Clin Cancer Res* 2002;**8**:1681–94
260. Pui CH, Relling MV, Downing JR. Acute lymphoblastic leukemia. *N Engl J Med* 2004;**350**:1535–48
261. Gaynon PS, Carrel AL. Glucocorticosteroid therapy in childhood acute lymphoblastic leukemia. *Adv Exp Med Biol* 1999;**457**:593–605
262. Kaspers GJ, Pieters R, Klumper E, De Waal FC, Veerman AJ. Glucocorticoid resistance in childhood leukemia. *Leuk Lymphoma* 1994;**13**:187–201
263. Schrappe M, Reiter A, Zimmermann M, Harbott J, Ludwig WD, Henze G, Gadner H, Odenwald E, Riehm H. Long-term results of four consecutive trials in childhood ALL performed by the ALL-BFM study group from 1981 to 1995. Berlin-Frankfurt-Munster. *Leukemia* 2000;**14**:2205–22
264. Tissing WJ, Meijerink JP, den Boer ML, Brinkhof B, van Rossum EF, van Wering ER, Koper JW, Sonneveld P, Pieters R. Genetic variations in the glucocorticoid receptor gene are not related to glucocorticoid resistance in childhood acute lymphoblastic leukemia. *Clin Cancer Res* 2005;**11**:6050–6
265. Morris SW, Kirstein MN, Valentine MB, Dittmer K, Shapiro DN, Look AT, Saltman DL. Fusion of a kinase gene, ALK, to a nucleolar protein gene, NPM, in non-Hodgkin's lymphoma. *Science* 1995;**267**:316–7
266. Cessna MH, Zhou H, Sanger WG, Perkins SL, Tripp S, Pickering D, Daines C, Coffin CM. Expression of ALK1 and p80 in inflammatory myofibroblastic tumor and its mesenchymal mimics: a study of 135 cases. *Mod Pathol* 2002;**15**:931–8
267. Gascoyne RD, Lamant L, Martin-Subero JI, Lestou VS, Harris NL, Muller-Hermelink HK, Seymour JF, Campbell LJ, Horsman DE, Auvigne I, Espinos E, Siebert R, Delsol G. ALK-positive diffuse large B-cell lymphoma is associated with Clathrin-ALK rearrangements: report of 6 cases. *Blood* 2003;**102**:2568–73
268. Jazii FR, Najafi Z, Malekzadeh R, Conrads TP, Ziaee AA, Abnet C, Yazdznbod M, Karkhane AA, Salekdeh GH. Identification of squamous cell carcinoma associated proteins by proteomics and loss of beta tropomyosin expression in esophageal cancer. *World J Gastroenterol* 2006;**12**:7104–12
269. Soda M, Choi YL, Enomoto M, Takada S, Yamashita Y, Ishikawa S, Fujiwara S, Watanabe H, Kurashina K, Hatanaka H, Bando M, Ohno S, Ishikawa Y, Aburatani H, Niki T, Sohara Y, Sugiyama Y, Mano H. Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. *Nature* 2007;**448**:561–6
270. Li R, Morris SW. Development of anaplastic lymphoma kinase (ALK) small-molecule inhibitors for cancer therapy. *Med Res Rev* 2008;**28**:372–412
271. Gu L, Gao J, Li Q, Zhu YP, Jia CS, Fu RY, Chen Y, Liao QK, Ma Z. Rapamycin reverses NPM-ALK-induced glucocorticoid resistance in lymphoid tumor cells by inhibiting mTOR signaling pathway, enhancing G1 cell cycle arrest and apoptosis. *Leukemia* 2008;**22**:2091–6
272. Marzec M, Kasprzycka M, Liu X, Raghunath PN, Wlodarski P, Wasik MA. Oncogenic tyrosine kinase NPM/ALK induces activation of the MEK/ERK signaling pathway independently of c-Raf. *Oncogene* 2007;**26**:813–21
273. Vega F, Medeiros LJ, Leventaki V, Atwell C, Cho-Vega JH, Tian L, Claret FX, Rassidakis GZ. Activation of mammalian target of rapamycin signaling pathway contributes to tumor cell survival in anaplastic lymphoma kinase-positive anaplastic large cell lymphoma. *Cancer Res* 2006;**66**:6589–97
274. Fan S, el-Deiry WS, Bae I, Freeman J, Jondle D, Bhatia K, Fornace AJ Jr, Magrath I, Kohn KW, O'Connor PM. p53 gene mutations are associated with decreased sensitivity of human lymphoma cells to DNA damaging agents. *Cancer Res* 1994;**54**:5824–30
275. Foroutan B, Ali Ruf A, Jerwood D, Anderson D. In vitro studies of DNA damage and its repair in cells from NHL patients with different p53 mutant protein status, resistant (p53(+)) and sensitive (p53(−)) to cancer chemotherapy. *J Pharmacol Toxicol Methods* 2007;**55**:58–64
276. Kerbauy FR, Colleoni GW, Saad ST, Silva MRR, Alves AC, Aguiar KC, Albuquerque DM, Kobarg J, Seixas MT, Kerbauy J. Detection and possible prognostic relevance of p53 gene mutations in diffuse large B-cell lymphoma. *An analysis of 51 cases and review of the literature.* Leuk Lymphoma 2004;**45**:2071–8
277. Drexler HG, Fombonne S, Matsuo Y, Hu ZB, Hamaguchi H, Uphoff CC. p53 alterations in human leukemia-lymphoma cell lines: in vitroartifact or prerequisite for cell immortalization? *Leukemia* 2000;**14**:198–206
278. Ichikawa A, Kinoshita T, Watanabe T, Kato H, Nagai H, Tsushita K, Saito H, Hotta T. Mutations of the p53 gene as a prognostic factor in aggressive B-cell lymphoma. *N Engl J Med* 1997;**337**:529–34
279. Moller MB, Gerdes AM, Skjodt K, Mortensen LS, Pedersen NT. Disrupted p53 function as predictor of treatment failure and poor prognosis in B- and T-cell non-Hodgkin's lymphoma. *Clin Cancer Res* 1999;**5**:1085–91
280. Koduru PR, Raju K, Vadmal V, Menezes G, Shah S, Susin M, Kolitz J, Broome JD. Correlation between mutation in p53, p53 expression, cytogenetics, histologic type, and survival in patients with B-cell non-Hodgkin's lymphoma. *Blood* 1997;**90**:4078–91
281. Happo L, Cragg MS, Phipson B, Haga JM, Jansen ES, Herold MJ, Dewson G, Michalak EM, Vandenberg CJ, Smyth GK, Strasser A, Cory S, Scott CL. Maximal killing of lymphoma cells by DNA damage-inducing therapy requires not only the p53 targets Puma and Noxa, but also Bim. *Blood* 2010;**116**:5256–67
282. Adams J. The development of proteasome inhibitors as anticancer drugs. *Cancer Cell* 2004;**5**:417–21
283. Richardson PG, Mitsiades C, Hideshima T, Anderson KC. Proteasome inhibition in the treatment of cancer. *Cell Cycle* 2005;**4**:290–6
284. Orlowski RZ, Kuhn DJ. Proteasome inhibitors in cancer therapy: lessons from the first decade. *Clin Cancer Res* 2008;**14**:1649–57
285. Stapnes C, Doskeland AP, Hatfield K, Ersvaer E, Ryningen A, Lorens JB, Gjertsen BT, Bruserud O. The proteasome inhibitors bortezomib and PR-171 have antiproliferative and proapoptotic effects on primary human acute myeloid leukaemia cells. *Br J Haematol* 2007;**136**:814–28
286. Strauss SJ, Higginbottom K, Juliger S, Maharaj L, Allen P, Schenkein D, Lister TA, Joel SP. The proteasome inhibitor bortezomib acts independently of p53 and induces cell death via apoptosis and mitotic catastrophe in B-cell lymphoma cell lines. *Cancer Res* 2007;**67**:2783–90
287. Meister S, Schubert U, Neubert K, Herrmann K, Burger R, Gramatzki M, Hahn S, Schreiber S, Wilhelm S, Herrmann M, Jack HM, Voll RE. Extensive immunoglobulin production sensitizes myeloma cells for proteasome inhibition. *Cancer Res* 2007;**67**:1783–92
288. Obeng EA, Carlson LM, Gutman DM, Harrington WJ Jr, Lee KP, Boise LH. Proteasome inhibitors induce a terminal unfolded protein response in multiple myeloma cells. *Blood* 2006;**107**:4907–16
289. McConkey DJ, Zhu K. Mechanisms of proteasome inhibitor action and resistance in cancer. *Drug Resist Updat* 2008;**11**:164–79
290. Fisher RI, Bernstein SH, Kahl BS, Djulbegovic B, Robertson MJ, de Vos S, Epner E, Krishnan A, Leonard JP, Lonial S, Stadtmauer EA, O'Connor OA, Shi H, Boral AL, Goy A. Multicenter phase II study of bortezomib in patients with relapsed or refractory mantle cell lymphoma. *J Clin Oncol* 2006;**24**:4867–74
291. Goy A, Younes A, McLaughlin P, Pro B, Romaguera JE, Hagemeister F, Fayad L, Dang NH, Samaniego F, Wang M, Broglio K, Samuels B,

Gilles F, Sarris AH, Hart S, Trehu E, Schenkein D, Cabanillas F, Rodriguez AM. Phase II study of proteasome inhibitor bortezomib in relapsed or refractory B-cell non-Hodgkin's lymphoma. *J Clin Oncol* 2005;**23**:667–75

292. O'Connor OA, Wright J, Moskowitz C, Muzzy J, MacGregor-Cortelli B, Stubblefield M, Straus D, Portlock C, Hamlin P, Choi E, Dumetrescu O, Esseltine D, Trehu E, Adams J, Schenkein D, Zelenetz AD. Phase II clinical experience with the novel proteasome inhibitor bortezomib in patients with indolent non-Hodgkin's lymphoma and mantle cell lymphoma. *J Clin Oncol* 2005;**23**:676–84
293. Ruckrich T, Kraus M, Gogel J, Beck A, Ovaa H, Verdoes M, Overkleeft HS, Kalbacher H, Driessen C. Characterization of the ubiquitin-proteasome system in bortezomib-adapted cells. *Leukemia* 2009;**23**:1098–105
294. Glas R, Bogyo M, McMaster JS, Gaczynska M, Ploegh HL. A proteolytic system that compensates for loss of proteasome function. *Nature* 1998;**392**:618–22
295. Princiotta MF, Schubert U, Chen W, Bennink JR, Myung J, Crews CM, Yewdell JW. Cells adapted to the proteasome inhibitor 4-hydroxy-5-iodo-3-nitrophenylacetyl-Leu-Leu-leucinal-vinyl sulfone require enzymatically active proteasomes for continued survival. *Proc Natl Acad Sci USA* 2001;**98**:513–8
296. Turk V, Turk B, Turk D. Lysosomal cysteine proteases: facts and opportunities. *EMBO J* 2001;**20**:4629–33
297. Li J, Lee AS. Stress induction of GRP78/BiP and its role in cancer. *Curr Mol Med* 2006;**6**:45–54
298. Mozos A, Roue G, Lopez-Guillermo A, Jares P, Campo E, Colomer D, Martinez A. The expression of the endoplasmic reticulum stress sensor BiP/GRP78 predicts response to chemotherapy and determines the efficacy of proteasome inhibitors in diffuse large B-cell lymphoma. *Am J Pathol* 2011;**179**:2601–10
299. Esteller M. Epigenetics in cancer. *N Engl J Med* 2008;**358**:1148–59
300. Ropero S, Esteller M. The role of histone deacetylases (HDACs) in human cancer. *Mol Oncol* 2007;**1**:19–25
301. Yang XJ, Seto E. The Rpd3/Hda1 family of lysine deacetylases: from bacteria and yeast to mice and men. *Nat Rev Mol Cell Biol* 2008;**9**:206–18
302. Kikuchi J, Wada T, Shimizu R, Izumi T, Akutsu M, Mitsunaga K, Noborio-Hatano K, Nobuyoshi M, Ozawa K, Kano Y, Furukawa Y. Histone deacetylases are critical targets of bortezomib-induced cytotoxicity in multiple myeloma. *Blood* 2010;**116**:406–17
303. Maiso P, Carvajal-Vergara X, Ocio EM, Lopez-Perez R, Mateo G, Gutierrez N, Atadja P, Pandiella A, San Miguel JF. The histone deacetylase inhibitor LBH589 is a potent antimyeloma agent that overcomes drug resistance. *Cancer Res* 2006;**66**:5781–9
304. Marks PA, Richon VM, Rifkind RA. Histone deacetylase inhibitors: inducers of differentiation or apoptosis of transformed cells. *J Natl Cancer Inst* 2000;**92**:1210–16
305. Sakai E, Bottaro A, Alt FW. The Ig heavy chain intronic enhancer core region is necessary and sufficient to promote efficient class switch recombination. *Int Immunol* 1999;**11**:1709–13
306. Marks P, Rifkind RA, Richon VM, Breslow R, Miller T, Kelly WK. Histone deacetylases and cancer: causes and therapies. *Nat Rev Cancer* **1**:194–202
307. Schreiber SL, Bernstein BE. Signaling network model of chromatin. *Cell* 2002;**111**:771–8
308. Kim MS, Kwon HJ, Lee YM, Baek JH, Jang JE, Lee SW, Moon EJ, Kim HS, Lee SK, Chung HY, Kim CW, Kim KW. Histone deacetylases induce angiogenesis by negative regulation of tumor suppressor genes. *Nat Med* 2001;**7**:437–43
309. Mitsiades CS, Mitsiades NS, McMullan CJ, Poulaki V, Shringarpure R, Hideshima T, Akiyama M, Chauhan D, Munshi N, Gu X, Bailey C, Joseph M, Libermann TA, Richon VM, Marks PA, Anderson KC. Transcriptional signature of histone deacetylase inhibition in multiple myeloma: biological and clinical implications. *Proc Natl Acad Sci USA* 2004;**101**:540–5
310. Duan H, Heckman CA, Boxer LM. Histone deacetylase inhibitors down-regulate bcl-2 expression and induce apoptosis in t(14;18) lymphomas. *Mol Cell Biol* 2005;**25**:1608–19
311. Bhalla S, Balasubramanian S, David K, Sirisawad M, Buggy J, Mauro L, Prachand S, Miller R, Gordon LI, Evens AM. PCI-24781 induces caspase and reactive oxygen species-dependent apoptosis through NF-kappaB mechanisms and is synergistic with bortezomib in lymphoma cells. *Clin Cancer Res* 2009;**15**:3354–65
312. Dasmahapatra G, Lembersky D, Kramer L, Fisher RI, Friedberg J, Dent P, Grant S. The pan-HDAC inhibitor vorinostat potentiates the activity of the proteasome inhibitor carfilzomib in human DLBCL cells in vitro and in vivo. *Blood* 2010;**115**:4478–87
313. Shimizu R, Kikuchi J, Wada T, Ozawa K, Kano Y, Furukawa Y. HDAC inhibitors augment cytotoxic activity of rituximab by upregulating CD20 expression on lymphoma cells. *Leukemia* 2010;**24**:1760–8
314. Aaltonen LA, Peltomaki P, Leach FS, Sistonen P, Pylkkanen L, Mecklin JP, Jarvinen H, Powell SM, Jen J, Hamilton SR, Petersen GM, Kinzler KW, Vogelstein B, Chapelle A de la. Clues to the pathogenesis of familial colorectal cancer. *Science* 1993;**260**:812–6
315. Fishel R, Lescoe MK, Rao MR, Copeland NG, Jenkins NA, Garber J, Kane M, Kolodner R. The human mutator gene homolog MSH2 and its association with hereditary nonpolyposis colon cancer. *Cell* 1993;**75**:1027–38
316. Ionov Y, Peinado MA, Malkhosyan S, Shibata D, Perucho M. Ubiquitous somatic mutations in simple repeated sequences reveal a new mechanism for colonic carcinogenesis. *Nature* 1993;**363**:558–61
317. Peltomaki P, Lothe RA, Aaltonen LA, Pylkkanen L, Nystrom-Lahti M, Seruca R, David L, Holm R, Ryberg D, Haugen A, Brøgger A, Børresen A, Chapelle A de la. Microsatellite instability is associated with tumors that characterize the hereditary non-polyposis colorectal carcinoma syndrome. *Cancer Res* 1993;**53**:5853–5
318. Thibodeau SN, Bren G, Schaid D. Microsatellite instability in cancer of the proximal colon. *Science* 1993;**260**:816–9
319. Miyashita K, Fujii K, Yamada Y, Hattori H, Taguchi K, Yamanaka T, Yoshida MA, Okamura J, Oda S, Muta K, Nawata H, Takayanagi R, Uike N. Frequent microsatellite instability in non-Hodgkin lymphomas irresponsive to chemotherapy. *Leuk Res* 2008;**32**:1183–95
320. Eckstein N, Servan K, Hildebrandt B, Politz A, von Jonquieres G, Wolf-Kummeth S, Napierski I, Hamacher A, Kassack MU, Budczies J, Beier M, Dietel M, Royer-Pokora B, Denkert C, Royer HD. Hyperactivation of the insulin-like growth factor receptor I signaling pathway is an essential event for cisplatin resistance of ovarian cancer cells. *Cancer Res* 2009;**69**:2996–3003
321. Williams RT, den Besten W, Sherr CJ. Cytokine-dependent imatinib resistance in mouse BCR-ABL+, Arf-null lymphoblastic leukemia. *Genes Dev* 2007;**21**:2283–7
322. Bajenoff M, Egen JG, Koo LY, Laugier JP, Brau F, Glaichenhaus N, Germain RN. Stromal cell networks regulate lymphocyte entry, migration, and territoriality in lymph nodes. *Immunity* 2006;**25**:989–1001
323. Okada T, Ngo VN, Ekland EH, Forster R, Lipp M, Littman DR, Cyster JG. Chemokine requirements for B cell entry to lymph nodes and Peyer's patches. *J Exp Med* 2002;**196**:65–75
324. Meads MB, Hazlehurst LA, Dalton WS. The bone marrow microenvironment as a tumor sanctuary and contributor to drug resistance. *Clin Cancer Res* 2008;**14**:2519–26
325. Linderoth J, Eden P, Ehinger M, Valcich J, Jerkeman M, Bendahl PO, Berglund M, Enblad G, Erlanson M, Roos G, Cavallin-Stahl E. Genes associated with the tumour microenvironment are differentially expressed in cured versus primary chemotherapy-refractory diffuse large B-cell lymphoma. *Br J Haematol* 2008;**141**:423–32
326. Walker A, Taylor ST, Hickman JA, Dive C. Germinal center-derived signals act with Bcl-2 to decrease apoptosis and increase clonogenicity of drug-treated human B lymphoma cells. *Cancer Res* 1997;**57**:1939–45
327. Taylor ST, Hickman JA, Dive C. Survival signals within the tumour microenvironment suppress drug-induced apoptosis: lessons learned from B lymphomas. *Endocr Relat Cancer* 1999;**6**:21–3
328. Shu HB, Hu WH, Johnson H. TALL-1 is a novel member of the TNF family that is down-regulated by mitogens. *J Leukoc Biol* 1999;**65**:680–3
329. Mercurio F, DiDonato JA, Rosette C, Karin M. p105 and p98 precursor proteins play an active role in NF-kappa B-mediated signal transduction. *Genes Dev* 1993;**7**:705–18

330. Naumann M, Wulczyn FG, Scheidereit C. The NF-kappa B precursor p105 and the proto-oncogene product Bcl-3 are I kappa B molecules and control nuclear translocation of NF-kappa B. *EMBO J* 1993;**12**:213–22
331. Lwin T, Crespo LA, Wu A, Dessureault S, Shu HB, Moscinski LC, Sotomayor E, Dalton WS, Tao J. Lymphoma cell adhesion-induced expression of B cell-activating factor of the TNF family in bone marrow stromal cells protects non-Hodgkin's B lymphoma cells from apoptosis. *Leukemia* 2009;**23**:170–7
332. Briones J, Timmerman JM, Hilbert DM, Levy R. BLyS and BLyS receptor expression in non-Hodgkin's lymphoma. *Exp Hematol* 2002;**30**:135–41
333. A predictive model for aggressive non-Hodgkin's lymphoma. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. *N Engl J Med* 1993;**329**:987–94
334. Dive C, Hickman JA. Drug-target interactions: only the first step in the commitment to a programmed cell death? *Br J Cancer* 1991;**64**:192–6
335. Raff MC. Social controls on cell survival and cell death. *Nature* 1992;**356**:397–400
336. Reed JC. Double identity for proteins of the Bcl-2 family. *Nature* 1997;**387**:773–6
337. Taylor ST, Hickman JA, Dive C. Epigenetic determinants of resistance to etoposide regulation of Bcl-X(L) and Bax by tumor microenvironmental factors. *J Natl Cancer Inst* 2000;**92**:18–23
338. Trikha M, Corringham R, Klein B, Rossi JF. Targeted anti-interleukin-6 monoclonal antibody therapy for cancer: a review of the rationale and clinical evidence. *Clin Cancer Res* 2003;**9**:4653–65
339. Gilbert LA, Hemann MT. DNA damage-mediated induction of a chemoresistant niche. *Cell* 2010;**143**:355–66
340. Trentin L, Cabrelle A, Facco M, Carollo D, Miorin M, Tosoni A, Pizzo P, Binotto G, Nicolardi L, Zambello R, Adami F, Agostini C, Semenzato G. Homeostatic chemokines drive migration of malignant B cells in patients with non-Hodgkin lymphomas. *Blood* 2004;**104**:502–8
341. Burger JA, Burger M, Kipps TJ. Chronic lymphocytic leukemia B cells express functional CXCR4 chemokine receptors that mediate spontaneous migration beneath bone marrow stromal cells. *Blood* 1999;**94**:3658–67
342. Burkle A, Niedermeier M, Schmitt-Graff A, Wierda WG, Keating MJ, Burger JA. Overexpression of the CXCR5 chemokine receptor, and its ligand, CXCL13 in B-cell chronic lymphocytic leukemia. *Blood* 2007;**110**:3316–25
343. Sipkins DA, Wei X, Wu JW, Runnels JM, Cote D, Means TK, Luster AD, Scadden DT, Lin CP. In vivo imaging of specialized bone marrow endothelial microdomains for tumour engraftment. *Nature* 2005;435969–73
344. Burger JA, Kipps TJ. Chemokine receptors and stromal cells in the homing and homeostasis of chronic lymphocytic leukemia B cells. *Leuk Lymphoma* 2002;**43**:461–6
345. Lenz G, Wright G, Dave SS, Xiao W, Powell J, Zhao H, Xu W, Tan B, Goldschmidt N, Iqbal J, Vose J, Bast M, Fu K, Weisenburger DD, Greiner TC, Armitage JO, Kyle A, May L, Gascoyne RD, Connors JM, Troen G, Holte H, Kvaloy S, Dierickx D, Verhoef G, Delabie J, Smeland EB, Jares P, Martinez A, Lopez-Guillermo A, Montserrat E, Campo E, Braziel RM, Miller TP, Rimsza LM, Cook JR, Pohlman B, Sweetenham J, Tubbs RR, Fisher RI, Hartmann E, Rosenwald A, Ott G, Muller-Hermelink HK, Wrench D, Lister TA, Jaffe ES, Wilson WH, Chan WC, Staudt LM. Stromal gene signatures in large-B-cell lymphomas. *N Engl J Med* 2008;**359**:2313–23
346. Allen CD, Ansel KM, Low C, Lesley R, Tamamura H, Fujii N, Cyster JG. Germinal center dark and light zone organization is mediated by CXCR4 and CXCR5. *Nat Immunol* 2004;**5**:943–52
347. Reif K, Ekland EH, Ohl L, Nakano H, Lipp M, Forster R, Cyster JG. Balanced responsiveness to chemoattractants from adjacent zones determines B-cell position. *Nature* 2002;**416**:94–9
348. Springer TA. Traffic signals for lymphocyte recirculation and leukocyte emigration: the multistep paradigm. *Cell* 1994;**76**:301–14
349. Byers RJ, Sakhinia E, Joseph P, Glennie C, Hoyland JA, Menasce LP, Radford JA, Illidge T. Clinical quantitation of immune signature in follicular lymphoma by RT-PCR-based gene expression profiling. *Blood* 2008;**111**:4764–70
350. Dave SS, Wright G, Tan B, Rosenwald A, Gascoyne RD, Chan WC, Fisher RI, Braziel RM, Rimsza LM, Grogan TM, Miller TP, LeBlanc M, Greiner TC, Weisenburger DD, Lynch JC, Vose J, Armitage JO, Smeland EB, Kvaloy S, Holte H, Delabie J, Connors JM, Lansdorp PM, Ouyang Q, Lister TA, Davies AJ, Norton AJ, Muller-Hermelink HK, Ott G, Campo E, Montserrat E, Wilson WH, Jaffe ES, Simon R, Yang L, Powell J, Zhao H, Goldschmidt N, Chiorazzi M, Staudt LM. Prediction of survival in follicular lymphoma based on molecular features of tumor-infiltrating immune cells. *N Engl J Med* 2004;**351**:2159–69
351. Farinha P, Masoudi H, Skinnider BF, Shumansky K, Spinelli JJ, Gill K, Klasa R, Voss N, Connors JM, Gascoyne RD. Analysis of multiple biomarkers shows that lymphoma-associated macrophage (LAM) content is an independent predictor of survival in follicular lymphoma (FL). *Blood* 2005;**106**:2169–74
352. Lee CG, Das B, Lin TL, Grimes C, Zhang X, Lavezzi T, Huang L, Cole J, Yau L, Li L. A rare fraction of drug-resistant follicular lymphoma cancer stem cells interacts with follicular dendritic cells to maintain tumourigenic potential. *Br J Haematol* 2012;**158**:79–90
353. Cuvillier O, Pirianov G, Kleuser B, Vanek PG, Coso OA, Gutkind S, Spiegel S. Suppression of ceramide-mediated programmed cell death by sphingosine-1-phosphate. *Nature* 1996;**381**:800–3
354. Maceyka M, Payne SG, Milstien S, Spiegel S. Sphingosine kinase, sphingosine-1-phosphate, and apoptosis. *Biochim Biophys Acta* 2002;**1585**:193–201
355. Macchia M, Barontini S, Bertini S, Di Bussolo V, Fogli S, Giovannetti E, Grossi E, Minutolo F, Danesi R. Design, synthesis, and characterization of the antitumor activity of novel ceramide analogues. *J Med Chem* 2001;**44**:3994–4000
356. Bayerl MG, Bruggeman RD, Conroy EJ, Hengst JA, King TS, Jimenez M, Claxton DF, Yun JK. Sphingosine kinase 1 protein and mRNA are overexpressed in non-Hodgkin lymphomas and are attractive targets for novel pharmacological interventions. *Leuk Lymphoma* 2008;**49**:948–54
357. Ageberg M, Rydstrom K, Linden O, Linderoth J, Jerkeman M, Drott K. Inhibition of geranylgeranylation mediates sensitivity to CHOP-induced cell death of DLBCL cell lines. *Exp Cell Res* 2011;**317**:1179–91
358. Novick P, Zerial M. The diversity of Rab proteins in vesicle transport. *Curr Opin Cell Biol* 1997;**9**:496–504
359. Wright LP, Philips MR. Thematic review series: lipid posttranslational modifications. CAAX modification and membrane targeting of Ras. *J Lipid Res* 2006;**47**:883–91
360. Zerial M, McBride H. Rab proteins as membrane organizers. *Nat Rev Mol Cell Biol* 2001;**2**:107–17
361. Chitambar CR, Zahir SA, Ritch PS, Anderson T. Evaluation of continuous-infusion gallium nitrate and hydroxyurea in combination for the treatment of refractory non-Hodgkin's lymphoma. *Am J Clin Oncol* 1997;**20**:173–8
362. Keller J, Bartolucci A, Carpenter JT Jr, Feagler J. Phase II evaluation of bolus gallium nitrate in lymphoproliferative disorders: a Southeastern Cancer Study Group trial. *Cancer Treat Rep* 1986;**70**:1221–3
363. Straus DJ. Gallium nitrate in the treatment of lymphoma. *Semin Oncol* 2003;**30**:25–33
364. Warrell RP Jr, Coonley CJ, Straus DJ, Young CW. Treatment of patients with advanced malignant lymphoma using gallium nitrate administered as a seven-day continuous infusion. *Cancer* 1983;**51**:1982–7
365. Weick JK, Stephens RL, Baker LH, Jones SE. Gallium nitrate in malignant lymphoma: a Southwest Oncology Group study. *Cancer Treat Rep* 1983;**67**:823–5
366. Chitambar CR, Zivkovic Z. Uptake of gallium-67 by human leukemic cells: demonstration of transferrin receptor-dependent and transferrin-independent mechanisms. *Cancer Res* 1987;**47**:3929–34
367. Esserman L, Takahashi S, Rojas V, Warnke R, Levy R. An epitope of the transferrin receptor is exposed on the cell surface of high-grade but not low-grade human lymphomas. *Blood* 1989;**74**:2718–29
368. Habeshaw JA, Lister TA, Stansfeld AG, Greaves MF. Correlation of transferrin receptor expression with histological class and outcome in non-Hodgkin lymphoma. *Lancet* 1983;**1**:498–501

369. Harris WR, Pecoraro VL. Thermodynamic binding constants for gallium transferrin. *Biochemistry* 1983;**22**:292–9
370. Kiratli PO, Canpinar H, Ruacan S, Kansu E. Correlation of flow cytometric parameters and transferrin receptors with gallium-67 scintigraphic images in lymphoma patients. *Nucl Med Commun* 2000;**21**:925–31
371. Larson SM, Rasey JS, Allen DR, Nelson NJ, Grunbaum Z, Harp GD, Williams DL. Common pathway for tumor cell uptake of gallium-67 and iron-59 via a transferrin receptor. *J Natl Cancer Inst* 1980;**64**:41–53
372. Yang M, Kroft SH, Chitambar CR. Gene expression analysis of gallium-resistant and gallium-sensitive lymphoma cells reveals a role for metal-responsive transcription factor-1, metallothionein-2A, and zinc transporter-1 in modulating the antineoplastic activity of gallium nitrate. *Mol Cancer Ther* 2007;**6**:633–43
373. Shapiro-Shelef M, Calame K. Regulation of plasma-cell development. *Nat Rev Immunol* 2005;**5**:230–42
374. Shapiro-Shelef M, Lin KI, Savitsky D, Liao J, Calame K. Blimp-1 is required for maintenance of long-lived plasma cells in the bone marrow. *J Exp Med* 2005;**202**:1471–6
375. Gyory I, Fejer G, Ghosh N, Seto E, Wright KL. Identification of a functionally impaired positive regulatory domain I binding factor 1 transcription repressor in myeloma cell lines. *J Immunol* 2003;**170**:3125–33
376. Johnson K, Shapiro-Shelef M, Tunyaplin C, Calame K. Regulatory events in early and late B-cell differentiation. *Mol Immunol* 2005;**42**:749–61
377. Garcia JF, Roncador G, Sanz AI, Maestre L, Lucas E, Montes-Moreno S, Fernandez Victoria R, Martinez-Torrecuadrara JL, Marafioti T, Mason DY, Piris MA. PRDM1/BLIMP-1 expression in multiple B and T-cell lymphoma. *Haematologica* 2006;**91**:467–74
378. Friedman HS, Colvin OM, Kaufmann SH, Ludeman SM, Bullock N, Bigner DD, Griffith OW. Cyclophosphamide resistance in medulloblastoma. *Cancer Res* 1992;**52**:5373–8
379. Jones RJ, Barber JP, Vala MS, Collector MI, Kaufmann SH, Ludeman SM, Colvin OM, Hilton J. Assessment of aldehyde dehydrogenase in viable cells. *Blood* 1995;**85**:2742–6
380. Brennan SK, Meade B, Wang Q, Merchant AA, Kowalski J, Matsui W. Mantle cell lymphoma activation enhances bortezomib sensitivity. *Blood* 2010;**116**:4185–91
381. Corti S, Locatelli F, Papadimitriou D, Donadoni C, Salani S, Del Bo R, Strazzer S, Bresolin N, Comi GP. Identification of a primitive brain-derived neural stem cell population based on aldehyde dehydrogenase activity. *Stem Cell* 2006;**24**:975–85
382. Hess DA, Meyerrose TE, Wirthlin L, Craft TP, Herrbrich PE, Creer MH, Nolta JA. Functional characterization of highly purified human hematopoietic repopulating cells isolated according to aldehyde dehydrogenase activity. *Blood* 2004;**104**:1648–55
383. Jones RJ, Gocke CD, Kasamon YL, Miller CB, Perkins B, Barber JP, Vala MS, Gerber JM, Gellert LL, Siedner M, Lemas MV, Brennan S, Ambinder RF, Matsui W. Circulating clonotypic B cells in classic Hodgkin lymphoma. *Blood* 2009;**113**:5920–6
384. Matsui W, Huff CA, Wang Q, Malehorn MT, Barber J, Tanhehco Y, Smith BD, Civin CI, Jones RJ. Characterization of clonogenic multiple myeloma cells. *Blood* 2004;**103**:2332–6
385. Hilton J. Role of aldehyde dehydrogenase in cyclophosphamide-resistant L1210 leukemia. *Cancer Res* 2004;**44**:5156–60
386. Kastan MB, Schlaffer E, Russo JE, Colvin OM, Civin CI, Hilton J. Direct demonstration of elevated aldehyde dehydrogenase in human hematopoietic progenitor cells. *Blood* **75**:1947–50
387. Kohn FR, Sladek NE. Aldehyde dehydrogenase activity as the basis for the relative insensitivity of murine pluripotent hematopoietic stem cells to oxazaphosphorines. *Biochem Pharmacol* 1985;**34**:3465–71
388. Magni M, Shammah S, Schiro R, Mellado W, Dalla-Favera R, Gianni AM. Induction of cyclophosphamide-resistance by aldehyde-dehydrogenase gene transfer. *Blood* 1996;**87**:1097–103
389. Russo JE, Hilton J. Characterization of cytosolic aldehyde dehydrogenase from cyclophosphamide resistant L1210 cells. *Cancer Res* 1988;**48**:2963–8
390. Compagno M, Lim WK, Grunn A, Nandula SV, Brahmachary M, Shen Q, Bertoni F, Ponzoni M, Scandurra M, Califano A, Bhagat G, Chadburn A, Dalla-Favera R, Pasqualucci L. Mutations of multiple genes cause deregulation of NF-kappaB in diffuse large B-cell lymphoma. *Nature* 2009;**459**:717–21
391. Dunleavy K, Pittaluga S, Czuczman MS, Dave SS, Wright G, Grant N, Shovlin M, Jaffe ES, Janik JE, Staudt LM, Wilson WH. Differential efficacy of bortezomib plus chemotherapy within molecular subtypes of diffuse large B-cell lymphoma. *Blood* 2009;**113**:6069–76
392. Catley L, Weisberg E, Kiziltepe T, Tai YT, Hideshima T, Neri P, Tassone P, Atadja P, Chauhan D, Munshi NC, Anderson KC. Aggresome induction by proteasome inhibitor bortezomib and alpha-tubulin hyperacetylation by tubulin deacetylase (TDAC) inhibitor LBH589 are synergistic in myeloma cells. *Blood* 2006;**108**:3441–9
393. Dai Y, Chen S, Kramer LB, Funk VL, Dent P, Grant S. Interactions between bortezomib and romidepsin and belinostat in chronic lymphocytic leukemia cells. *Clin Cancer Res* 2008;**14**:549–58
394. Lewis TS, McCormick RS, Emmerton K, Lau JT, Yu SF, McEarchern JA, Grewal IS, Law CL. Distinct apoptotic signaling characteristics of the anti-CD40 monoclonal antibody dacetuzumab and rituximab produce enhanced antitumor activity in non-Hodgkin lymphoma. *Clin Cancer Res* 2011;**17**:4672–81
395. Hutter G, Rieken M, Pastore A, Weigert O, Zimmermann Y, Weinkauf M, Hiddemann W, Dreyling M. The proteasome inhibitor bortezomib targets cell cycle and apoptosis and acts synergistically in a sequence-dependent way with chemotherapeutic agents in mantle cell lymphoma. *Ann Hematol* 2012;**91**:847–56
396. Lancet JE, Duong VH, Winton EF, Stuart RK, Burton M, Zhang S, Cubitt C, Blaskovich MA, Wright JJ, Sebti S, Sullivan DM. A phase I clinical-pharmacodynamic study of the farnesyltransferase inhibitor tipifarnib in combination with the proteasome inhibitor bortezomib in advanced acute leukemias. *Clin Cancer Res* 2011;**17**:1140–6
397. Zhao XF, Gartenhaus RB. Phospho-p70S6K and cdc2/cdk1 as therapeutic targets for diffuse large B-cell lymphoma. *Expert Opinion Ther Targets* 2009;**13**:1085–93
398. Deng J, Carlson N, Takeyama K, Dal Cin P, Shipp M, Letai A. BH3 profiling identifies three distinct classes of apoptotic blocks to predict response to ABT-737 and conventional chemotherapeutic agents. *Cancer Cell* 2007;**12**:171–85

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