Novel Therapeutic Options in Anaplastic Large Cell Lymphoma: Molecular Targets and Immunological Tools

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Abstract

Anaplastic large cell lymphoma (ALCL) is a CD30-positive, aggressive T-cell lymphoma, and about half of the patients with this disease harbor the t(2;5)(p21;q35) translocation. This chromosomal aberration leads to fusion of the NPM gene with the ALK tyrosine kinase, leading to its constitutive activation. To date, treatment options include polychemotherapy (e.g., cyclophosphamide, doxorubicin, vincristine, and prednisone), which is sometimes combined with radiation in the case of bulky disease, leading to remission rates of ~80%. However, the remaining patients do not respond to therapy, and some patients experience chemo-resistant relapses, making the identification of new and better treatments imperative. The recent discovery of deregulated ALK in common cancers such as non–small cell lung cancer and neuroblastoma has reinvigorated industry interest in the development of ALK inhibitors. Moreover, it has been shown that the ALK protein is an ideal antigen for vaccination strategies due to its low expression in normal tissue. The characterization of microRNAs that are deregulated in ALCL will yield new insights into the biology of ALCL and open new avenues for therapeutic approaches in the future. Also, CD30 antibodies that have been tested in ALCL for quite a while will probably find a place in forthcoming treatment strategies. Mol Cancer Ther; 10(7); 1127–36. ©2011 AACR.

Introduction

Anaplastic large cell lymphoma (ALCL) is a rare, aggressive, mature T-cell lymphoma that affects both children and adults. ALCL accounts for 10% to 15% of all non-Hodgkin’s lymphoma (NHL) cases in children and 2% to 8% of NHL cases in adults. Clinically, ALCL can be distinguished as a systemic disease or a localized primary cutaneous entity. Systemic ALCL is a very aggressive lymphoma that involves different extranodal secondary sites, including soft tissue, skin, bone, lungs, and liver (1). Primary cutaneous ALCL accounts for <2% of the disease frequency but has a 5-year disease-free survival rate of ~90% upon standard treatment (2). The primary systemic and cutaneous subtypes have a similar histologic appearance, with so-called hallmark cells showing large cells with abundant cytoplasm and eccentric, lobulated nuclei (3). However, the clear distinction of ALCL from other disease entities was made possible by the work of Stein and colleagues (4), who showed that the surface antigen CD30 is expressed by ALCL cells. In about half of the patients, the translocation t(2;5)(p23;q35) can be found, resulting in the expression of the nucleophosmin-anaplastic lymphoma kinase (NPM-ALK) fusion protein. ALK+ lymphomas represent 50% to 85% of systemic ALCL cases and occur mainly in the first 3 decades of life, predominantly in males. ALK− ALCL occurs in older patients, with a peak at 60 years of age and lower male predominance. ALK− ALCL patients have a less favorable prognosis than ALK+ ALCL patients after treatment with polychemotherapy. Other fusion partners of the ALK kinase, such as tropomyosin-3, 5-aminomimidazole-4-carboxamide ribonucleotide formyltransferase/IMP cyclohydrolase, clathrin heavy chain, and TRK fused gene 1, have been described (Fig. 1). In most cases, the fusion partners contain a dimerization domain that leads to constitutive activation of the ALK kinase (5). NPM is a multifunctional 23 kDa protein that is involved in diverse processes such as ribosome biogenesis, regulation of cell division, and DNA repair. ALK is a trans-membrane receptor tyrosine kinase (RTK) of the insulin receptor superfamily (6). The normal function of ALK is still elusive, especially because knockout mice have only very subtle phenotypes. In normal tissue, ALK expression has mainly been found in the neonatal brain, peripheral nervous system, and spinal fluid, suggesting a function in neuronal development.

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Note: The website for the European Research Initiative on Anaplastic Large Cell Lymphoma is www.erialcl.net

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The fusion of the N-terminal part of NPM to the kinase domain of ALK results in its constitutive activation. This leads to the activation of multiple downstream pathways, including PI3K/Akt/mTOR (7), JAK/Stat3 (8), c-myc (9), and cjun/JunB (ref. 10; Fig. 1). Mouse models that express the NPM-ALK within the hematopoietic system have shown the transforming capacity of this fusion protein (10–12). However, it remains a mystery why the ALCL variant that does not bear the translocation has the worst prognosis. The skewed age distribution, with adult ALCL patients often lacking the NPM-ALK translocation, may influence the perception of a more negative outcome for ALK negative patients. In patients older than 40 years, a prognostic difference between the ALK+ and ALK- variants of ALCL has not been found (13). In the most recent World Health Organization classification of this disease, the ALK+ and ALK- subgroups were classified as 2 different disease entities, mainly due to their different prognostic properties (14). The molecular features of ALK-negative ALCL are largely unknown. Interest in
ALK kinase activation and its functional consequences increased tremendously after the recent finding that the echinoderm microtubule-associated protein-like 4-ALK kinase fusion protein (EML4-ALK) can be detected in >6% of non–small cell lung cancer (NSCLC) patients (15). Soda and colleagues (16) developed a mouse model for EML4-ALK–driven lung cancer and showed that ALK inhibitors can be effectively used for treatment in the murine system. By the end of 2009, Pfizer had launched a phase 3 clinical trial evaluating ALK inhibitors for the treatment of NSCLC bearing the EML4-ALK fusion. In patients with neuroblastoma (NB), point mutations were found that resulted in constitutive ALK activation in 6% to 12% of the patients (17–20). Recently, the EML4-ALK translocation was found with the use of exon array detection in 80% of patients. Approximately 60% of ALK+ patients only enter remission following CHOP treatment, leaving room for improvement of treatment strategies.

ALK Kinase Inhibitors

The ALK cDNA encodes a protein of 177 kDa. The protein contains an extracellular ligand–binding domain, a transmembrane–spanning region, and a cytoplasmic kinase catalytic part (the TK domain), which has a major autophosphorylation site that regulates the conformation of the activation loop (Fig. 1). Full–length endogenous ALK supports tumor formation in NBs and glioblastomas, where it is suggested to be activated by the ligands pleiotropin and midkine (22, 23); however, the importance of the ligands is under debate (24). In ALCL and NSCLC, ALK is activated by chromosomal rearrangements leading to the fusion of the ALK gene to another gene, resulting in its dimerization and persistent activation. In NB, specific activating mutations within the gene, resulting in its dimerization and persistent activation, were not successful, which may be due to the long half-life (>48 h) of the NPM-ALK protein (25). Piva and colleagues (26) found that antagonizing the NPM-ALK mRNA with small hairpin RNA through retroviral transfection was a more successful approach and established the essential function of this fusion protein in the proliferation of ALK+ cell lines in vivo as well as in a murine ALCL engraftment model.

The ALK inhibitors staurosporine and 7-hydroxystaurosporine (UCN-01) are natural products that are isolated from Streptomyces staurosporosus. UCN-01 was reported to have antitumor activity in a single patient with ALK-positive ALCL that was refractory to conventional CHOP therapy (27). Derivatives of staurosporine include the inhibitors CEP-14083 and CEP-14513 (Cephalon, Frazer, PA), whose clinical use is hampered by unfavorable physical properties such as low solubility and stability (28, 29). Second–generation inhibitors, such as compound 18 (Cephalon, Frazer, PA), showed improved properties in vivo with oral bioavailability and effective inhibition of tumor growth in the SCID mouse Sup-M2 tumor xenograft model (30). Another class of naturally occurring ALK modulators consists of 17–allylamino–17–demethoxypyrrolidinoalkaloids such as geldanamycin (17–AAG), geldanamycin, and herbimycin A. These modulators lead to indirect ALK inhibition via binding to heat shock protein 90 (HSP-90), thereby enhancing the proteasome–mediated degradation of the ALK protein (31, 32). Other inhibitor classes include pyridine, thiazole, aminopyridine, diaminoypyridine, and fused ring systems. Li and colleagues (33) identified a series of novel pyridones as kinase inhibitors of ALK by stepwise in vitro screening followed by iterative template modification and computational ranking. One substance in this inhibitor family is the Novartis compound NVP-TAE684, which inhibits proliferation of Karpas-299 and SU-DHL-1 cell lines with an IC50 range of 2 to 5 nM, hindering autophosphorylation of NPM-ALK (34). This compound is highly NPM-ALK specific, as the activity of other insulin receptor kinases is not significantly impaired. Another member of this inhibitor class is the GlaxoSmithKline compound GS1138705, which is an ATP–competitive inhibitor of ALK, insulin–like growth factor (IGF)–1R, and insulin receptor (35). This compound is of special interest because of its good pharmacokinetic properties and excellent oral bioavailability (see Table 1 and Fig. 2).

The only compound currently undergoing clinical testing is the Pfizer compound PF-02341066 (crizotinib; Fig. 2), which was initially developed as an inhibitor of c-Met (36) but was found to have a similar IC50 for ALK (24 nM). In vitro, it showed antiproliferative activity in ALCL cell lines (Karpas-299 and SU-DHL-1) leading to cell cycle arrest and apoptosis. The rather moderate side effects were predicted by the fact that it could be administered repeatedly in mice, dogs, and primates at concentrations up to 200 mg/kg/day for up to 30 days (36). It was tested in a monotherapy trial in heavily pretreated NSCLC patients with tumors harboring a rearrangement of EML4-ALK. The overall response rate was 64% and the disease control rate reached 90%, with a median duration of treatment of 25.5 weeks (37). Based on these promising results, at the end of 2009, Pfizer began to screen 1,500 patients with NSCLC for ALK translocations. Eighty-two (5.5%) of these patients had an ALK translocation (although in some cases not involving EML4) and were therefore eligible for PF-02341066 (crizotinib) treatment. It is interesting to note that this patient subgroup consisted mostly of relatively young nonsmokers with...
CD30 Antibodies

CD30 is a trans-membrane protein that belongs to the tumor necrosis factor receptor family. It is expressed on activated (but not resting) B and T cells, and in addition to its expression on ALCL cells, it can also be found on Reed-Sternberg cells in Hodgkin’s lymphoma (HL). CD30 antibodies and derivatives were tested in patients with this disease >15 years ago. In one of the first promising studies, the anti-CD30 monoclonal antibody was bound to saporin, a protein with ribosome-inactivating activity. This immunotoxin was given to 4 patients with pretreated, refractory HL. In 3 of 4 patients, a rapid reduction of tumor mass was observed; however, the clinical responses were transient (41). In patients with HL and NHL, investigators attempted to bind CD30 to the toxin ricin or $^{131}$I. However, the presence of side effects such as decreases in serum albumin, edema, and hypotension with the ricin, or severe hematotoxicity in the case of the Iodine-131-coupled antibody, dampened the enthusiasm for these types of treatments (42–44). In a seminal phase 1/2 study by Ansell and colleagues (45), it was shown that a fully human anti-CD30 immunoglobulin G1 monoclonal antibody (MDX-060) was well tolerated at concentrations up to 15 mg/kg in a mixed patient population, including patients with HL and ALCL. Despite high expectations, however, only 6 of 72 patients showed a clinical response. In a more recent study with 39 heavily pretreated HL patients (82% of whom had failed at least one prior therapy regimen) and 41 systemic ALCL patients using the anti-CD30 antibody SGN-30 (Seattle Genetics), none of the HL patients had an objective response (46). In contrast, in the ALCL arm, 2 patients achieved a complete response (4.9%) and 5 showed a partial response (12%), pointing to a limited clinical activity of this antibody. Side effects were rather mild, with fatigue and nausea being the most frequently reported symptoms. In a phase 2 study in which the same antibody was tested in CD30-positive, heavily pretreated patients with cutaneous ALCL, lymphomatoid papulosis, and transformed mycosis fungoides, SGN-30 showed clinical activity (complete or partial response) in 16 out of 23 patients. Specifically, in cutaneous ALCL, clinical activity was seen in all patients, with responses in 82% of the treated patients (47). These are encouraging results, especially given the mild side-effects profile. However, these data have to be considered in context with current treatment strategies using pegylated liposomal doxorubicin and gemcitabine, which have response rates for cutaneous ALCL ranging from 69% to 80% (48). The latest
addition to these CD-30 antibody-based treatment strategies is SGN-35 (brentuximab vedotin; Seattle Genetics). In this case, the CD-30 antibody is coupled to the antitubulin agent monomethyl auristatin E (MMAE) with an enzyme-cleavable dipeptide linker. This drug has been tested in 42 patients with CD30-positive relapsed or refractory HL (n = 40) or ALCL (n = 2) patients with a median of 3 previous therapy regimens. It is remarkable that in 36 of 42 patients (86%) tumor regression was observed, and among the 11 complete remissions, 2 systemic ALK+ ALCL cases were found (49). The success of this coupled antibody is even more surprising in light of the limited activity of the CD30 antibody alone (SGN-30) in systemic ALCL, and stresses the role of the attached cytoskeleton toxin. Another appealing feature of the armed CD-30 antibody strategy is that, in contrast to ALK inhibitors,
it can be used in all subtypes of ALCL, including ALK− ALCL, ALK+ ALCL, and cutaneous ALCL.

Inhibitors of NPM-ALK-Activated Downstream Pathways

ALK hyperactivation potentiates a multitude of partially overlapping mitogenic cellular pathways that lead to transformation, proliferation, and cell survival. The main activated pathways include the PI3K/Akt/mTOR, ras-ERK, and JAK/STAT pathways (ref. 1; see also Fig. 1). JAK3, for example, is a lymphocyte-specific member of the Janus kinase signal transducer family that is expressed in ALCL cells but not in resting T cells. JAK3 is a signal transducer from ALK to STAT3, which in turn activates antiapoptotic proteins within the bcl2-rheostat such as Bcl2, Bcl-XL, and Mcl1, as well as cyclins, C-EBPβ, and survivin. Several JAK3 small-molecule inhibitors, including PF-956980 (Pfizer), have been described (50, 51). SHP1 is a phosphatase tumor suppressor that is constitutively deactivated through promoter methylation in 50% of ALK+ ALCL, and deactivates the JAK3/STAT3 pathway. Using the methyl-transferase inhibitor 5-aza-deoxycytidine, Han and colleagues (52) showed that SHP1 could be reactivated, leading to reduced levels of JAK3, p-JAK3, and p-STAT3, and sensitized cells to doxorubicin-induced apoptosis. Also, a small-molecule (S3I-201) that directly deactivates STAT3 by inhibiting DNA binding and STAT3 complex formation, identified from the National Cancer Institute chemical library, has been described and may be of therapeutic interest (53).

For the STAT3 downstream targets Bcl2 and Bcl-XL, a potent inhibitor called ABT-737 has been developed by Abbott Laboratories, and a derivate of this inhibitor, ABT-236 (navitoclax; Abbott Laboratories), which is orally available, has also been described (54, 55). Overexpression of the related Mcl1 protein has often been described as conferring resistance to ABT-737 and ABT-263; therefore, it is tempting to speculate that the reintroduction of microRNAs (miRNAs) that are down-regulated in ALCL and target Mcl1, such as miR-101 and miR-29b, might sensitize ALCL cells to the effect of Bcl-2 inhibitors. The ras-ERK pathway, which is mainly responsible for cell proliferation, may be inhibited by farnesyltransferase or geranylgeranyltransferase inhibitors (56). The Akt/mTOR pathway is one of the most prominent pathways that are often overactivated in cancer. Therefore, multiple approaches have been described to inhibit its activity. In the case of AKT, classical ATP competitive inhibitors, phosphatidyl analogs that block the essential binding of AKT to PI(3,4,5)P3, pseudosubstrate inhibitors, and allosteric inhibitors have been described (57). The mTOR protein can be selectively suppressed by rapamycin and its orally available analog, temsirolimus. The feasibility of this strategy was demonstrated in ALCL mouse models, in which temsirolimus was shown to effectively reduce tumor growth (58).

miRNAs and ALCL

miRNAs are small, evolutionary conserved, noncoding RNAs that have been described to regulate the expression of target genes through translational inhibition or mRNA degradation. To date, ~1,000 miRNAs have been described in humans, and it is predicted (based on computational algorithms) that they are involved in regulating ~30% of the proteins that are transcribed from the human genome (59, 60). The roles of miRNAs are as diverse as their targeted proteins, and therefore there are almost no aspects of cancer biology that are not affected by miRNAs. Investigators have described oncogenic miRNAs (miR-21 and miR-17–92 cluster), as well as miRNAs that act as tumor suppressors (miR-34a, miR-15a/16–1, and miR-29a, b,c). To complicate the issue, one miRNA can play tremendously different roles depending on its cellular context. For example, miR-34a, which is a downstream target of p53, is overexpressed in CLL (61) but is down-regulated in NSCLC, glioblastoma, and NB, raising the question as to whether it is a tumor suppressor or an oncogene. Until recently, the role of miRNAs in ALCL was undefined. We did a comprehensive screen of deregulated miRNA expression in human formalin-fixed, paraffin-embedded (FFPE) tissue samples, a murine ALCL tumor model, and 5 ALCL cell lines. miR-101 was down-regulated in primary ALCL FFPE tissues, the ALCL mouse model, and all tested ALCL cell lines. When miR-101 was reintroduced into the ALCL cell lines, we observed a reduced proliferation of ALK+ but not ALK− cell lines. When we inhibited the described miR-101 target mTOR using the rapamycin analog temsirolimus, we found that proliferation of the ALK+ ALCL cell lines was inhibited much more strongly than that of the ALK− cell lines, suggesting a stronger dependence of ALK+ cell lines on the mTOR pathway. Moreover, we identified miRNAs that are differentially expressed in ALK+ versus ALK− ALCL. Members of the oncogenic miR-17–92 cluster were more strongly expressed in ALK+, whereas the oncogenic miR-155, coded within the B-cell integration cluster RNA, was expressed 10-fold higher in ALK+ ALCL (Fig. 1). Given the poor prognosis for ALCL patients who do not bear the ALCL. Members of the oncogenic miR-17–92 cluster were more strongly expressed in ALK+, whereas the oncogenic miR-155, coded within the B-cell integration cluster RNA, was expressed 10-fold higher in ALK+ ALCL (Fig. 1). Given the poor prognosis for ALCL patients who do not bear the ALK translocation (with a 5-year survival of only 30%–40%), the need for new treatment options is obvious. miRNA-155 has been linked to B-cell differentiation, oncogenesis, and immune function, making it the first molecular therapeutic target for ALK− ALCL (62–64).

Vaccination Strategies

In the years since some groundbreaking studies introduced the concept of cancer immune surveillance through the innate and adapted immune systems of patients, many studies have followed up on this concept and dramatically increased our knowledge about the interactions between the immune system and cancer (65-67). In general, the control of cancer by the immune system, often called immune editing, consists
of 3 phases: elimination, equilibrium, and evasion. Elimination of tumor cells through the immune system involves building a balance between tumor growth and immune response, resulting in a small, undetectable amount of tumor cells. In the equilibrium phase, the tumor is held in check by antibodies and thus is unable to grow. In the evasion phase, the tumor, either by suppressing the immune response or by editing its exposed antigens, is able to escape the immune system and grow into a clinically apparent cancer (68). Ideally, an antigen that is used for vaccination would be specifically expressed in the tumor; it must have an important, causal part in the multifactorial process that leads to cancer, and it must be expressed stably even after it is attacked by the immune system. As highly specific antigens for tumor vaccination, one could envisage the protein products of mutated tumor suppressors, as well as proteins encoded by oncogenic viruses. However, these strictly tumor-specific antigens are relatively rare, and therefore researchers have widened their spectrum of target antigens to tumor-associated antigens, which in many cases are lineage markers that are also expressed on the corresponding healthy cells. Sipuleucel-T (Dendreon Corporation), a vaccine for prostate cancer that is based on ex vivo stimulation of patients’ monocytes with a fusion protein consisting of prostatic acid phosphatase and granulocyte macrophage colony-stimulating factor, received Food and Drug Administration approval in April 2010. Furthermore, melanoma and other epithelial cancers are being investigated in phase 1/2 trials (68). It is clear that only ALCL forms that bear the ALK translocation would be amenable to this type of treatment. Given the above-mentioned preconditions for a tumor antigen, ALK is an ideal target for potential tumor vaccination. First, with the exception of the immunoprivileged central and peripheral nervous systems, the ALK kinase is not expressed, or is expressed at very low levels, in normal tissues. Second, it has been shown that the ALK kinase has a strong transforming capacity in normal T cells and can cause cancer in transgenic animal models, where the NPM-ALK fusion protein is specifically expressed in CD4 T cells or bone marrow (10–12). These facts have led many groups to test various strategies for tumor vaccination in murine ALCL model systems. The ALK-fusion proteins have immunogenic properties per se, hence Pulford and colleagues (69) showed that antibodies against ALK can be found in patients with ALK-positive ALCL. In a more recent study (70), the same group showed that these antibodies can persist for >10 years after the ALCL has been cured in a patient, and it is likely that these antibodies will remain present for the rest of that person’s life. ALK-specific antibodies were observed in 87 of 95 chemo-naïve ALCL patients, and it was shown that high antibody titers correlated with a reduced incidence of relapse. Given the positive prognostic value of the ALK translocation within the ALCL patient cohort, it has been hypothesized that this may be due to a permanent antitumor immune response toward the ALK-fusion protein in these patients.

Efforts to actively tune the immune response toward ALK have also been undertaken. In a study by Passoni and colleagues (71), 2 ALK-derived, HLA-A*0201-binding peptides were able to elicit an ALK-specific cytotoxic T-lymphocyte response in peripheral blood mononuclear cells of HLA-matched healthy donors and in transgenic mice bearing the human HLA-A*0201 locus. Moreover, the anti-ALK-peptide–primed cytotoxic T cells were able to lyse HLA-matched ALCL and NB cell lines that expressed the ALK protein.

In a different approach using DNA vaccination, Chiarle and colleagues (72) electroporated Balb/C mice twice with a plasmid containing the intracytoplasmic domain of ALK. The great advantage of DNA vaccination, as opposed to vaccination with HLA-specific peptides, is that it can be done independently of the HLA haplotype. One week after the last immunization, the mice were injected with $1 \times 10^6$ cells of an ALCL, ALK+ cell line. Of interest, the vaccinated animals were completely protected from ALCL engraftment, and this protection remained present for >70 days. However, when the immunization was carried out after engraftment of the ALCL cells, the attenuating effect on tumor growth was minimal. Therefore, the authors tried to debulk the tumor using 1 bolus of doxorubicin, followed by vaccination on days 7, 14, and 21 after administration of the doxorubicin bolus. The chemotherapy alone led to a remission rate of 60%, which was further enhanced by additional vaccination to 87%. This suggests the feasibility of using a vaccination strategy after a tumor is debulked by classical chemotherapy.

Conclusions

Despite the relative success of classical chemotherapy (together with radiation) in ALCL, it is clear that novel treatments are needed for resistant or relapsing patients. Furthermore, it seems that the concept of TK inhibition, which has shown success in chronic myeloid leukemia [i.e., with imatinib (Gleevec; Roche)], may also hold promise for other cancers, including ALCL. This is substantiated by recent successful clinical trials of the ALK-TK inhibitor crizotinib in solid tumor entities such as NSCLC and IMT (38, 40), which leaves us optimistic about its effectiveness in NB and ALCL. However, we have to await the results of clinical trials that are currently being done. Also, the CD30 antibody-based therapeutic strategies that have been tested for a long time with only limited success are far from dead. The recent clinical trial with the armed CD30 antibody SGN-35 showed that this approach not only holds promise but translated into complete clinical responses in 10/40 heavily pretreated HL and 2/2 ALK+ ALCL patients. It is important to note that this agent may also be active in ALK- ALCL patients,
in whom ALK kinase inhibitors are useless. It is clear that the treatment of ALK− ALCL patients remains a big challenge for the future. To date, not much is known about the specific molecular properties of ALK− ALCL that might be instrumental in developing new drugs. Recently, overexpression of the oncogenic miR-155 and a chromosomal translocation t(6;7)(p25.3;q32.3) resulting in miR-29 activation was reported in this class of patients (58, 73). The recent increase in the therapeutic armamentarium for lymphomas should give us confidence that also in the context of ALK− ALCL, which up to now has proved resistant to the identification of specific molecular targets, basic research elucidating novel genetic and immunologic features will allow the development of new and more-effective treatment options.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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5. Webb TR, Slavish J, George RE, Look AT, Xue L, Jiang Q, et al. The recent increase in the therapeutic armamentarium for lymphomas should give us confidence that also in the context of ALK− ALCL, which up to now has proved resistant to the identification of specific molecular targets, basic research elucidating novel genetic and immunologic features will allow the development of new and more-effective treatment options.

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