Antisense therapy in oncology: new hope for an old idea?

Ingo Tamm, Bernd Dörken, Gunther Hartmann

There is a potential role for antisense oligonucleotides in the treatment of disease. The principle of antisense technology is the sequence-specific binding of an antisense oligonucleotide to target mRNA, resulting in the prevention of gene translation. The specificity of hybridisation makes antisense treatment an attractive strategy to selectively modulate the expression of genes involved in the pathogenesis of diseases. One antisense drug has been approved for local treatment of cytomegalovirus-induced retinitis, and several antisense oligonucleotides are in clinical trials, including oligonucleotides that target the mRNA of BCL2, protein-kinase-C alpha, and RAF kinase. Antisense oligonucleotides are well tolerated and might have therapeutic activity. Here, we summarise treatment ideas in this field, summarise clinical trials that are being done, discuss the potential contribution of CpG motif-mediated effects, and look at promising molecular targets to treat human cancer with antisense oligonucleotides.
expression was proven. These observations were particularly important because they encouraged the notion that antisense oligonucleotides could be used in living cells to manipulate gene expression. The introduction of efficient methods for DNA sequencing and oligonucleotide synthesis led to much activity in the field of antisense research. One of the first published studies to show in-vivo activity of oligonucleotides was done by Whitesell and colleagues. The group infused a phosphodiester oligonucleotide directed toward the antisense target sequence in the gene of interest.

### Rational drug design

Generally, the essential steps in rational drug design are identification of an appropriate target responsible for a certain disease and development of a drug with specific recognition and affinity to that target. For most drugs the mechanism of action is not well defined. By contrast, the specificity of Watson-Crick hybridisation is the basis for rational drug design of antisense oligonucleotides, leading to a new class of selective protein synthesis inhibitors. At the same time, the elucidation of the pathogenetic role of individual target proteins for certain diseases is rapidly progressing, most notably in cancer research.

Since antisense oligonucleotides inhibit gene expression in a sequence specific way, selective alteration of the expression of genes by use of closely related sequences is possible. The antisense strategy allows the detailed analysis of signal transduction pathways, which often comprise groups of highly homologous proteins. Furthermore, research with oligonucleotides might lead to the identification of new therapeutic targets and provide a corresponding drug at the same time. Because most tumour cells have a different pattern of gene expression by comparison with normal cells, antisense oligonucleotides can theoretically be used to specifically target tumour-associated genes, or mutated genes, without altering gene expression of normal cells.

### Clinical trials

The number of clinical trials ongoing represents a growing interest in antisense technology (panel 2). Generally, systemic treatment with antisense oligonucleotides is well tolerated and side-effects are dose-dependent. Dose-limiting toxicities include thrombocytopenia, hypotension, fever, and asthenia. Furthermore, an increase in concentration of the liver enzymes aspartate aminotransferase and alanine aminotransferase, as well as complement activation and a prolonged partial thromboplastin time, have been reported.

In 1998, the first antisense drug (fomivirsen) was approved by the US Food and Drugs Administration (FDA) for the treatment of cytomegalovirus-induced retinitis in patients with AIDS. The inhibitory constant (IC\(_{50}\)) of fomivirsen for cytomegalovirus-replication in vitro is 0.06 \(\mu\)mol/L, for ganciclovir the IC\(_{50}\) is 30-fold higher (2 \(\mu\)mol/L). Although fomivirsen is administered locally (intravitreal injection), FDA approval shows the feasibility of antisense oligonucleotides as drugs for the treatment of human diseases.

Most of the proteins involved in the pathogenesis of cancer operate inside the cell, and are thus not accessible to protein-based drugs. To target the genes, which code for those proteins, by use of antisense oligonucleotides, requires a unique target sequence in the gene of interest...
and the design of a complementary oligonucleotide against the target sequence that confers biological activity.16

G3139
The BCL2 group of proteins is a promising target for an antisense approach in oncology. BCL2 is an apoptosis inhibitor, which was discovered as a proto-oncogene located at the breakpoints of t(14;18) chromosomal translocations in low-grade B-cell non-Hodgkin’s lymphomas. BCL2 is overexpressed in most follicular lymphomas, in some diffuse large-cell lymphomas, and in chronic lymphocytic leukaemia.17 The oncogenic impetus of raised Bcl2 expression was verified in Bcl2 transgenic mice. These mice accumulated excess non-cycling mature B lymphocytes.18 High concentrations of BCL2 are associated with relapse in acute myelogenous leukaemia and in acute lymphocytic leukaemia.19 The BCL2 group of proteins has been implicated not only in the pathogenesis of cancer but also in resistance to cancer treatment. Anticancer drugs and radiation ultimately destroy cells by induction of apoptosis. BCL2 blocks caspase activation in tumour cells at the mitochondrial stage, which prevents apoptosis induced by radiation and available chemotherapeutic drugs.20

In a phase I study,6 the pharmacokinetics, toxicity, and therapeutic activity of an antisense oligonucleotide targeting the mRNA of BCL2 was assessed. 21 patients with BCL2-positive relapsed non-Hodgkin’s lymphoma were given a 14-day subcutaneous infusion of an 18-mer phosphorothioate oligonucleotide complementary to the target sequence that confers biological activity.38

For personal use. Only reproduce with permission from The Lancet Publishing Group.
in mice. The dose-limiting toxicities were thrombocytopenia and fatigue at a dose of 3-0 mg/kg per day. Evidence of tumour response lasting up to 11 months was seen in three of four patients with ovarian cancer.

Updated results of a phase I/II trial of ISIS 3521 combined with carboplatin and paclitaxel in patients with stage IIIb or IV non-small-cell lung cancer (NSCLC) have been reported.44,45 In 24 evaluable patients with NSCLC, 46% had a partial response and 33% had a minor response or stable disease. The median time to progression was 6-5 months. The 1 year survival was 78% with a median survival of 18 months. Typical survival of patients receiving standard chemotherapy alone is about 8 months. Toxicity consisted of neutropenia (grade 3 in six patients and grade 4 in eight patients) and thrombocytopenia (grade 3 in six patients and grade 4 in two patients). Thus, the combination of ISIS 3521, carboplatin, and paclitaxel was well tolerated, and showed promising activity in NSCLC. On the basis of these results, a 600-patient, randomised phase III clinical trial of ISIS 3521 in combination with chemotherapy for NSCLC has started.

Alavi and colleagues46 tested the efficacy, toxicity, and pharmacology of ISIS 3521 delivered as a 21 day continuous intravenous infusion in patients with high grade astrocytomas. Toxicities were mild and reversible. There is no evidence of a clinical benefit so far. Median time to progression was 35 days after entering the protocol and median survival was 93 days.

ISIS 5132

Other attractive targets for antisense therapy in oncology are RAF kinases and RAS. RAF kinases are serine/threonine kinases that regulate mitotic signalling pathways, most notably the mitogen-activated protein kinase pathway that transmits signals from RAS. C-RAF has been reported to bind to BCL2 and to be involved in the regulation of apoptosis. The RAS oncogene is deregulated or mutated more frequently than any other oncogene studied in human cancer.47,48 In several tumours, including breast and NSCLC, the expression of RAS is a prognostic factor.49 In pancreatic cancer, for which standard therapy is strikingly ineffective, 95% of all cases show RAS mutations.49 This finding suggests that alterations in this pathway play a significant part in the pathogenesis of cancer.

An antisense oligonucleotide directed to the 3’-untranslated region of the c-RAF1 mRNA (ISIS 5132) inhibited the growth of human tumour cell lines in vitro and in vivo in association with specific down-regulation of target message expression. In a phase I trial, changes in c-RAF1 mRNA expression were analysed in peripheral blood mononuclear cells collected from patients with advanced cancers treated with ISIS 5132. Significant reductions of c-RAF1 expression from baseline were detected in 13 of 14 patients. Two patients, both of whom had shown tumour progression with previous cytotoxic chemotherapy, exhibited long-term stable disease in response to treatment with antisense oligonucleotides. The researchers suggest that peripheral blood mononuclear cells can be used to confirm antisense-mediated inhibition of the target protein in vivo.50 However, the decrease in c-RAF1 expression in total peripheral blood mononuclear cells could represent changes in the proportion of leucocyte populations due to non-antisense-mediated immunomodulation, so this method does not provide proof for an antisense specific effect.

In a phase I trial, 31 patients with advanced malignancies received ISIS 5132 as a 2-h intravenous infusion three times every week for 3 consecutive weeks, with doses ranging from 0-5 to 6-0 mg/kg.51 Clinical toxicities included fever and fatigue, neither of which were dose limiting. Two patients experienced prolonged disease stabilisation for more than 7 months. In both of these cases, this stabilisation was associated with reduction in c-RAF1 expression in peripheral blood mononuclear cells.

Cunningham and co-workers52 reported the results of a trial testing continuous intravenous infusion of ISIS 3132 for 21 days every 4 weeks in 34 patients with various solid tumours refractory to standard therapy. Toxicities up to 4-0 mg/kg were not dose limiting. Doses of 2-0–4-0 mg/kg are comparable to doses in mice at which activity was seen in human xenograft models. Grade 3 fever arose in two of 34 patients treated. One patient treated with 5-0 mg/kg had fever as a dose-limiting toxicity. Three patients developed grade 3 or 4 thrombocytopenia and one had grade 3 leucopenia. Two patients developed sepsis; one of them, while septic, manifested grade 4 thrombocytopenia, grade 4 hyperbilirubinemia, and a grade 3 increase in aspartate aminotransferase, the other developed grade 4 thrombocytopenia. Leucopenia was mild, and no patient had neutropenia. One patient with ovarian cancer refractory to therapy had a large reduction in concentrations of the cancer biomarker CA125 (97%)53, and two other patients had prolonged disease stabilisation for 9 and 10 months.

Phase II trials of ISIS 5132 have begun. There is no evidence of single agent activity of ISIS 5132 in pretreated patients with recurrent ovarian cancer.54 In one study, 22 patients were treated at a dose of 4 mg/kg daily by 21-day continuous intravenous infusion every 4 weeks. ISIS 5132 was well tolerated with no grade 3 or 4 haematological or biochemical toxicity. There were six documented episodes of grade 3 non-haematological toxicity (two lethargy, one anorexia, two pain, one shortness of breath). No objective clinical response was seen. Three patients had stable disease for a median of 3-8 months, and the other evaluable patients had documented progressive disease. No patient had a decrease in CA125 of 50% or more. The outcome of other phase II clinical studies, including some in prostate and colon cancer, will be available shortly.

ISIS 2503

A 20-base phosphorothioate antisense oligonucleotide (ISIS 2503), which binds to the translation initiation region of human HRAS mRNA, selectively reduced the expression of HRAS mRNA and protein in cell culture. In a phase I trial, ISIS 2503 caused no dose-limiting toxicity at doses up to 10 mg/kg daily by 14-day continuous intravenous infusion. A non-toxic dose of 6 mg/kg daily was selected for further study. A phase II trial of ISIS 2503 as first line treatment for patients with untreated stage IV or recurrent colorectal carcinoma is in progress. In an interim analysis, 17 patients had received 38 cycles. Toxicity was limited to grade 1–2 fever and grade 1 thrombocytopenia in three patients. Two patients had stable disease after 3 and 6 cycles of treatment.55

C-MYB antisense oligonucleotide

Autologous transplantation has become part of the routine management of many haematological malignancies. However, many patients relapse after the procedure. Results of gene marking studies suggest that contamination of tumour cells, which are inadvertently reinfused with the graft, might contribute to relapse in acute myelogenous leukaemia and chronic myelogenous leukaemia. Antisense oligonucleotides against c-myb have been used to purge haematopoietic cell harvests from patients with chronic myelogenous leukaemia before...
immunodeficient and nude mice bearing xenografts of intraperitoneal administration, GEM 231 had dose-related ovarian and breast cancer patients. After oral or with worse clinicopathological features and prognosis in PKA is overexpressed in most human cancers, correlating concentration is increased in a wide variety of cancer cells. Several advanced chemical modifications have been used to improve specificity, pharmacokinetics, and safety of phosphorothioate oligonucleotides. MG 98 Hypermethylation by the enzyme DNA methyltransferase has been postulated to inactivate tumour suppressor genes, resulting in neoplastic transformation and tumorigenesis. Drugs that prevent or reverse DNA methylation might therefore restore control of growth of cancer cells. MG 98 is a phosphorothioate antisense oligonucleotide, which specifically inhibits translation of the mRNA for human DNA methyltransferase with an IC₅₀ of 50–70 nmol/L in tumour cell lines. Delay of tumour growth and tumour regression in response to MG 98 were seen in human lung and colon cancer xenografts. In a phase I study, researchers investigated the effect of MG 98 given as a continuous 21-day intravenous infusion administered at 4-week intervals. In an interim analysis, nine patients with solid cancers received ten courses of therapy at doses up to 240 mg/m² daily. Dose limiting drug-related increases of transaminases (grade 3) were encountered in two of two patients at the 240 mg/m² dose. Other toxicities were minor. Biologically relevant concentrations for the inhibition of human DNA methyltransferase mRNA were achieved with the lowest dose assessed (40 mg/m² daily). MG 98 is in phase II clinical trials.

**GEM 231**

Several advanced chemical modifications have been used to improve specificity, pharmacokinetics, and safety profiles of phosphorothioate oligonucleotides. Of note, these so-called mixed-backbone oligonucleotides permit oral and colorectal administration as a result of their increased in vivo metabolic stability. One of these compounds, GEM 231, was designed to provide optimum immune stimulation, are widely recognised as an undesirable side-effect of certain antisense oligonucleotides. Like other new technologies, antisense faces several methodological limitations, including oligonucleotide stability versus binding affinity, delivery of oligonucleotides to the target cells, and non-antisense effects of oligonucleotides. There has been good progress in antisense technology over the past years, and most of these issues have been addressed in reviews. Here, we will summarise information that has improved our understanding of non-antisense-mediated biological effects of oligonucleotides.

**Non-antisense action of oligonucleotides**

Like other new technologies, antisense faces several methodological limitations, including oligonucleotide stability versus binding affinity, delivery of oligonucleotides to the target cells, and non-antisense effects of oligonucleotides. There has been good progress in antisense technology over the past years, and most of these issues have been addressed in reviews. Here, we will summarise information that has improved our understanding of non-antisense-mediated biological effects of oligonucleotides.

Immune stimulation is widely recognised as an undesirable side-effect of certain antisense oligonucleotides, which can interfere with therapeutic activity. With respect to the clinical application of oligonucleotides, in this review we concentrate on their stimulatory effects in the human immune system. The immunostimulatory activity of unmodified phosphodiester oligonucleotides is strongly dependent on the presence of unmethylated CG dinucleotides in certain base contexts, so-called CpG motifs. Of note, the phosphorothioate backbone, which is generally used in antisense oligonucleotides to provide stability against nucleases, has immunostimulating properties itself, which are independent of the sequence. The immunostimulatory activity of a phosphorothioate-modified oligonucleotide is largely unpredictable, and has to be ascertained experimentally. Strong immunostimulatory activity is likely if the sequence starts with a TC at the 5’ end, and if the sequence contains CG dinucleotides (e.g., CpG ODN205, prototype to stimulate human immune cells). Immune stimulation might be avoided in antisense oligonucleotides by the selection of CG-free target sequences, by the use of oligonucleotide backbones that do not support immune stimulation, or by selective methylation of the cytosine in any CG dinucleotide.

CpG-dependent immune stimulation of a DNA molecule represents a highly evolved immune detection mechanism whose actual goal is the detection of microbial nucleic acids. By contrast with vertebrate DNA, in which CpG dinucleotides are suppressed and highly methylated, microbial genomes do not generally feature CpG suppression or methylation. Immune effector cells, such as B cells and dendritic cells, seem to have evolved pattern recognition receptors that, by binding the microbe-restricted structure of CpG motifs, trigger protective immune responses. CpG oligonucleotides, which are designed to provide optimum immune stimulation, are promising anticancer drugs. They are being tested in several clinical trials including ones for non-Hodgkin lymphoma, melanoma, basal cell carcinoma, and kidney cancer. Although specific immune activation by an oligonucleotide seems to have various potential therapeutic applications, it is generally undesirable in antisense oligonucleotides.

Several of the most advanced antisense oligonucleotides in clinical trials against cancer contain CG dinucleotides. An antisense oligonucleotide directed against the mRNA of BCL2 (G3139) and used in some of the clinical trials...
described above contains two CG dinucleotides and a TC at the 5’ end. It is noteworthy that this sequence was successfully used as an immunostimulatory CpG oligonucleotide in animal tumour models. Klasa and colleagues showed that G3139 has reduced but still considerable therapeutic activity in a human lymphoma xenograft in severe combined immune deficient mice, which lack T cells and natural killer cells. From their results the authors concluded that the therapeutic activity of this oligonucleotide is largely due to an antisense mechanism. However, macrophages, which are still present in these immunodeficient mice, might contribute to the antitumour activity of this antisense oligonucleotide. Furthermore, an oligonucleotide with the same sequence as G3139 directly induced activation and differentiation of primary human non-Hodgkin lymphoma cells by a CpG-dependent mechanism. Even if a tumour (ie, melanoma) is not sensitive to direct CpG-mediated activation, CpG-induced stimulation of the immune system might still be involved in eliminating the tumour in vivo. Thus, the relative contribution of a specific antisense mechanism versus immune stimulation, particularly of G3139, is still controversial.

New targets

There are several new potential targets for specific antisense treatment of human cancer. The inhibitor of apoptosis (IAP) family of proteins constitute a group of apoptosis suppressors (XIAP, c-IAP1, c-IAP2, NAIP, survivin, apollon, livin), which are conserved throughout animal evolution, with homologues in flies, worms, mice, and people. These proteins function as direct inhibitors of certain caspases. Since caspases are central for most apoptotic pathways, the fact that IAPs protect cells from several anticancer drugs and other inducers of apoptosis is not surprising. c-IAP2 at 11q21, and a newly discovered gene, MLT at 18q21, are involved in t(11;18)(q21;q21) associated with mucosa-associated lymphoid tissue (MALT) lymphoma. The translocation suggests a role for c-IAP2 in the pathogenesis of MALT-lymphoma, since this rearrangement occurs in about 50% of low-grade MALT-lymphomas. Antisense oligonucleotides that target either the c-IAP2/MLT breakpoint or one of the two partners involved in the fusion protein in MALT-lymphoma cells, could potentially alter the antiapoptotic function of c-IAP2 and induce cell death in MALT-lymphoma cells.

Another antiapoptosis molecular target is survivin. Survivin is overexpressed in a large proportion of human cancers, providing evidence that altered expression of these proteins occurs during tumorigenesis. In colorectal, gastric, breast, bladder, and lung cancers, as well as in diffuse large B-cell lymphoma, survivin expression is associated with shorter survival. In neuroblastoma, survivin expression correlates with a high stage of disease. Interestingly, survivin is expressed in a cell cycle dependent manner, with highest concentrations in G2/M and rapid downregulation after cell cycle arrest. At the beginning of mitosis, survivin associates with the mitotic spindle. Disruption of this interaction results in a loss of its antiapoptotic function. Some researchers have suggested that survivin frees cyclin dependent kinase 4 (CDK4) from the cyclin dependent kinase inhibitor, p16 CDK4 then translocates into the nucleus where it initiates the S-phase of the cell cycle. The overexpression of survivin in cancer might thus overcome cell cycle checkpoints and favour aberrant progression of transformed cells through mitosis. Survivin, therefore, bridges apoptosis and cell cycle. Mutation of a conserved cysteine in the survivin baculovirus-inhibitory repeat (BIR) domain abolishes the cytoprotective abilities of survivin. However, the BIR mutant retains the ability to associate with microtubules similar to wild-type survivin, and interferes with the function of endogenous survivin by competing for microtubule binding. Thus, in contrast to p53, which links DNA replication in the S phase of the cell cycle to apoptosis, survivin seems to couple the cell-suicide response to the checkpoint machinery involved in later cell-cycle steps (G2/M). An antisense oligonucleotide, targeting nucleotides 232–251 of human survivin mRNA, has been shown to induce apoptosis in lung cancer cell lines, and to sensitize cells to chemotherapy. Moreover, blockade of survivin expression induces apoptosis in myeloma cell lines.

Other potentially interesting targets are proteins collectively known as heat shock proteins (HSP). HSPs are among the most conserved proteins known and include a number of different families. Among the best analysed HSPs are HSP70 and HSP27. These two proteins possess cytoprotective activity and are frequently overexpressed in human cancer. Results of gene transfer experiments have shown that HSP70 and HSP27 not only confer resistance against heat stress, but also against most apoptotic stimuli such as tumour necrosis factor, ceramide, ultraviolet radiation, caspase-3 overexpression, and several chemotherapeutic drugs. HSP expression in certain cancer types correlates with poor prognosis and resistance to treatment. In breast cancer, HSP70 expression is a useful prognostic marker for much shorter disease-free survival, increased cell proliferation, and poor differentiation, as well as lymph node metastases. Furthermore, HSP70 inversely correlates with the response of breast cancer to combination chemotherapy. In ovarian cancer, HSP27 expression increases with advanced stage, and high HSP27 content in tumour cells is associated with greatly reduced survival. Similarly, HSP27 is a marker of poor prognosis in osteosarcoma. The data suggest that HSP27 and HSP70 are interesting new targets for a specific antisense-based tumour treatment.

Certain chromosome abnormalities, especially translocations, are associated with particular subtypes of leukaemia, lymphoma, and sarcoma. Among these are the translocations involving AML1 on 21q22, MLL on 11q23, and TEL on 12p13. Abnormalities of these genes account for a large proportion of patients with acute lymphocytic leukaemia and acute myelogenous leukaemia. Cloning of translocation breakpoints results in unique diagnostic tools for fluorescence in situ hybridisation and molecular analysis of leukaemic cells. Advances in understanding the alterations in the function of the fusion genes compared with normal genes provide insights with respect to new therapeutic strategies, including antisense therapy.

For personal use. Only reproduce with permission from The Lancet Publishing Group.
Thus, to target one causal gene with antisense oligonucleotides in leukaemia patients might be advantageous. The list of fusion proteins that might act as targets for antisense therapy in leukaemias and lymphomas is long and includes, for example, the translocation 4;11 in acute lymphocytic leukaemia, which is associated with a bad prognosis, and t(11;14) in mantle cell lymphoma. Other new targets for antisense therapy are involved in tumour cell proliferation, angiogenesis, and metastasis—eg, growth factor receptor tyrosine kinases such as the epidermal growth factor receptor; transcription factors such as NF-kB, HER-2/Neu, cyclin-dependent kinases, and telomerase (proliferation); the vascular endothelial growth factor receptor and the basic fibroblast growth factor receptor (angiogenesis); and matrix metalloproteinases, angiogenin and integrins (angiogenesis and metastasis).14,15

**Future perspectives**

New hope for the idea of antisense is provided by the results of a study done by Jansen and colleagues, which show that, besides the clinical benefit for patients with advanced melanoma, systemic treatment with antisense oligonucleotides results in the downregulation of the target protein within the target tissue. This study is a milestone in the field of antisense, since the results suggest that the principle of antisense works, not only with local treatment, as shown with fomivirsen, but also with systemic treatment with antisense oligonucleotides. If this study is seen as proof of principle, it might now pave the way for development of antisense oligonucleotides for various new potential targets for the treatment of cancer. Once the mechanism for one antisense oligonucleotide is established, the door is open for combination treatment with several oligonucleotides, targeting various oncogenes, to overcome tumour escape and to improve therapeutic activity of this approach.

However, careful assessment of future controlled studies is needed to confirm antisense-mediated downregulation of the target protein in a larger number of patients and for other antisense oligonucleotides. In the end, we might find that a sound proof of principle is virtually impossible in a clinical trial, because of limitations imposed by the lack of adequate controls. In addition to the possibility of specific antisense-mediated inhibition of the target oncogene, decreased concentrations of the oncogene would also be expected as a consequence of oligonucleotide-induced antitumour effects other than antisense.

Besides antisense-mediated inhibition of the target protein, one of the effects likely to be involved in antitumour action of certain antisense oligonucleotides is their immunostimulatory effect based on the presence of Cg dinucleotides within the sequence. Of note, the BCL2 protein, one of the effects likely to be involved in antitumour effects other than antisense, is expected as a consequence of oligonucleotide-induced antisense-mediated inhibition of the target oncogene, and adequate controls. In addition to the possibility of specific antisense-mediated inhibition of the target oncogene, decreased concentrations of the oncogene would also be expected as a consequence of oligonucleotide-induced antitumour effects other than antisense.

**References**


37 Wickstrom EL, Bacon TA, Gonzalez A, Freeman DL, Lyman GH, Wickstrom E. Human promyelocytic leukemia HL60 cell proliferation and c-MYC protein expression are inhibited by an antisense phosphorothioate oligonucleotide targeted against c-MYC mRNA. *Proc Natl Acad Sci USA* 1988; 85: 1028–32.


appropriate references and information for the review on the role of survivin in cancer. This includes discussions on the expression of survivin in various cancer types, its association with prognosis, and potential therapeutic strategies targeting survivin. The text also highlights the significance of survivin as a target for developing anti-cancer therapies.