Research Article

Targeting Apoptosis as a Therapeutic Approach in Cancer

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Abstract
Cancer is a major health problem worldwide, it has been known in its ability in evading and escaping apoptosis. All types of cancer cells gain resistance to apoptosis; they are prone to escape the normal cellular growth and death pathways result in uncontrollable division and proliferation. Apoptosis is programmed cell death or cell suicide; a process normally found in every eukaryotic cell. Damaged DNA triggers the cell to activate apoptotic machinery to remove itself from the body. Apoptosis is an extremely organized process: the cellular membranes are disrupted, the chromosomes are degraded, the DNA breaks up into fragments, and the dying shrinking cell is engulfed by immune cells in a clean and orderly manner. In this review, we will discuss the apoptotic pathways that can be used as a therapeutic target in cancer.

Keywords: apoptosis, apoptotic pathways, cancer, p53, cell cycle, cancer stem cell, miRNA.

Introduction
For decades, cancer has been one of the primary causes of death in all countries all over the world. According to the WHO, there were around 9.6 million deaths due to cancer in 2018 and 70% of such deaths occurred in low and middle income countries.

Currently, cancer management has multiple treatment strategies available; chemo- and radiotherapy and there is also surgery. Each treatment strategy has its significance and effectiveness in tumor cells which can be assessed by the ability to initiate the apoptosis cascade, thus, manipulate and restore the overexpressed anti-apoptotic proteins levels, and increase the expression of pro-apoptotic molecules could be the new goal of treatment. Recognizing the underlying mechanism of programmed cell death has created a new insight in cancer treatment by obtaining specific molecules that aim for a signal, gene and/or protein in cancer cells to promote its suicidal; meanwhile, non-harmful to the normally developed cells. In this article, we evaluate how apoptosis can be used as targeted therapy in cancer.

Apoptosis
Programmed cell death; apoptosis is a normal physiological process which is critical for life. Its significance relies in tumor suppression, maintaining tissue homoeostasis and infection resistance. The balance between cell proliferation and death must be maintained throughout life. Apoptosis; a strictly controlled complex process at the molecular level regulated by the balance between the pro- and anti-apoptotic proteins has the liability of clearing any damaged DNA containing cells out of the body. Both, the extrinsic and intrinsic initiators of the apoptotic pathways which lead to activation of caspases cascade conduct several and complete characteristic changes of cell morphology that undergoing apoptosis.

Morphological and Biochemical Changes in Apoptosis
Morphologically, apoptotic cell undergoes lessening in size, budding of plasma membrane while maintaining its integrity till the end, nucleic acid degradation and expression of phosphatidylserine on the outer layers of the membrane which allows early phagocytosis by macrophages to recognize, detect and engulf apoptotic cells in clear distinction manner than necrosis which usually accompanied by the presence of pro-inflammatory signals that would lead to cellular lysis and inflammation.

The organelles within the cells are prone to specific alterations in the morphological...
features that occur in the late stages of apoptosis, membrane blebbing can also be observed and the change in its asymmetry \(^8\).

Caspases; a family of proteases which is the main regulators and key players of apoptosis is synthesized as pro-caspases; inactive proteins \(^9\).

They are classified into initiators and executers/effectors. Initiators such as: caspase-2, -8, and 9 begin the apoptosis mechanism through the auto-activation and auto-cleavage of pro-caspases by an auto-proteolysis process, while executers such as caspase-3, -6 -7 and -10 proteolyze target substrate for the purpose of cell death. Since initiators are responsible for the beginning of the apoptosis mechanism, they start by binding to specific adaptor molecules to become activated \(^10, 11\).

Then, they activate executers' caspases which result in cytoplasmic endonuclease activation and chromatin condensation. This highly strict irreversible step represent the optimum goal of both extrinsic and intrinsic pathways \(^12\). This profound mechanism controlled by caspases is responsible of the features and morphological changes that occur during apoptosis, such as plasma budding, cytoplasmic blebbing and apoptotic bodies \(^13\). (Figure 1)

**Figure (1): Graphical illustration of intrinsic and extrinsic apoptotic pathways.**

**Targeting Bcl-2 Family**

One of the foremost vital pathways of apoptosis is mitochondria-dependent intrinsic pathway. Thus, targeting this pathway is practical approach to induce apoptosis \(^14\). Bcl-2 family is the key player of the intrinsic pathways, which either promote or suppress the permeability of mitochondrial membrane as needed for the release or blocking of cytochrome-c and other apoptotic proteins \(^15, 16\).

Since anti-apoptotic proteins work by inhibiting apoptosis and increasing the viability and the proliferation of the cells, it was reported in several studies that their over-expression is in correlation with tumor progression and development \(^17\).

Bcl-2 antisense (oblimersen sodium) is the first drug reported to target Bcl-2 pathway that entered clinical trials, Bcl-2 antisense decreased the mortality and increased the survival of chronic lymphocytic leukemia patients by increasing the sensitivity to chemotherapy drugs when both used in combination \(^18, 19\).

Another study suggested the use of ABT-263 (navitoclax) to target bcl-2 family which showed efficacy in clinical trials. It was suggested that combination strategy between ABT-263 with anthracyclines such as doxorubicin or with cyclin dependant kinase 9 inhibitors such as dinaciclib induced potent apoptosis in small cell lung cancer cell lines \(^20\). The use of navitoclax is limited by its major side effects of thrombocytopenia \(^21\).

BH3 mimetic anti-cancer drug has been approved by the FDA in 2016 under the name of venetoclax for treating chronic lymphocytic leukemia. BH3 mimetics bind to the bcl-2 freeing BIM. The freed BIM can then bind and sequester any unoccupied non-targeted anti-apoptotic protein and facilitates apoptosis \(^22\).
This drug does not cause thrombocytopenia while retaining proapoptotic activity (21).

Navitoclax and venetoclax have broad specificity against bcl-2 but not MCL1 (bcl-2 family member) as it has significant different binding site than bcl2. Obtaining a drug would target MCL1 is a target as it is one of the most commonly amplified genes across all cancer types (23).

The AM-8621 and VU661013, a spiromacro-cyclic ring with submolar binding affinity to the MCL1 groove displace BIM from MCL1, with lower binding affinity to BCL2 or BCL-xL (24). The disturbing in the interaction between BIM-MCL1 lead to activation of BAK and caspases and cause apoptosis induction.

Ramsey and his colleges showed the beneficial effect of using BCL2 and MCL1 inhibitors in sequence or in combination in acute myeloblastic leukemia clinical trials to induce apoptosis (25).

Also, small-molecule tyrosine kinase inhibitors (erlotinib, lapatinib) used to increase the sensitivity of navitoclax-mediated apoptosis, which caused MCL1 degradation. This increased MCL1 degradation can induce dramatic apoptotic responses (26).

Nangia and his colleges indicated that the combination therapy between MEK and MCL1 inhibition induces apoptosis and tumor suppression in KRAS mutant non-small cell lung cancer (NSCLC) which was synergized by the exposure to BCL-XL inhibitors at first, which promotes the binding of pro-apoptotic BCL-2 proteins to MCL-1 (27).

Graviola is a plant derived compound has been shown anticancer properties. A study revealed it inhibit BCL-2 proteins while increasing BAX and promoting apoptosis (28). The exact mechanism still not completely understood, but it shows promising activity as potential treatment in cancer.

**Targeting the Tumor Suppressor Gene P53**

There are multiple anticancer drugs would target p53 mediated pathways as it is an important tumor inhibitor and also pro-apoptotic protein that would initiate apoptosis. For decades, p53 has been known for its ability to initiate DNA repair by increasing the expression of specific target genes through binding to their regulatory sequences (29).

It is primary goal to repair damaged DNA, but if DNA is extensively damaged, cell cycle arrest or apoptosis will occur due to the activation of p53 (30). P53 function is essential to inhibit tumorgenesis.

Thus, many new anti-cancer strategies target the stimulation or the refolding of the mutant p53 pathway to induce cell death (31). This could be by targeting p53 itself or by using small molecules capable of restoring p53 functions. Also, aiming its target gene products, such as the pro-apoptotic Bax protein, which show ability to mediate apoptosis, inhibit Bcl-2 expression and initiate the intrinsic apoptotic pathway (32, 33).

P53 mutation and inactivation is observed in different tumor tissue, cells biopsies and cell lines which represent a relation between p53 mutation and tumor progression (34).

Based on a recent study by Sergiu and co-workers investigated the use of CRISPER/Cas system to restore the TP53 in tumor cells by completely replacing the mut-p53 with the functional copy in the human genome showed promising results in induction of cell suicide and apoptosis (35).

A compound that represents a breakthrough in the activation of mutant p53 thiosemicarbazones which was investigated by Yu and his colleges served as source of zinc for mut-p53. Wt-p53 contains zinc ion which is essential for the binding between the p53 and DNA domain. This drug allowed refolding of the mutant p53 to its wild type conformation and caused proper binding between the p53 and the DNA (36).

Also, testing polyarginine on p53 mutant cancer cells in vitro has been investigated by Kana-pathipillai. The results showed significant inhibition of polyarginine and polyornithine on p53 mutant peptide aggregation in vitro and growth inhibition of p53 mutant (R248Q) lung cancer cells H719 and p53 mutant (R175H) breast cancer cells SK-BR-3, with no effect on the wild type p53 and exhibit no toxicity on normal cells (37).
According to Wiman and co-workers, the use of PRIMA-1(p53-Reactivation and Induction of Massive Apoptosis-1); quinuclidine compound initiated the DNA binding activity in vitro in various cancer cells bearing mut-p53. This drug increased the expression of p53 target genes such as BAX, PUMA and NOXA and also activated caspases for apoptosis induction, and it’s methylated derivative; PRIMA-1Met caused better and promising results\(^{(36)}\).

Another drug for restoring the function of mut-p53 is MIRA-1 (mut-p53-dependent induction of rapid apoptosis). Although the chemical structures of MIRA and PRIMA-1 are distinct from each other, they have quit similar molecular mechanism for the re-activation of mut-p53\(^{(38)}\). They both alter thiol groups, while MIRA-1 induces cell death, caspase activation and apoptosis in mut-p53 dependant pathway much faster with higher potency than PRIMA-1 \(^{(39)}\).

According to a study by Sidharta Chatterjee, the scientist designed bioactive compound to block the signaling pathway between HDM2/MDM2 and p53 to increase p53 expression in cancer cells for apoptosis induction. MDM2 is a negative regulator for p53: it induces p53 fragmentation and inhibits p53 activity as a result of a binding between MDM2 and p53 \(^{(40)}\).

**Targeting the Extrinsic Cell Death**

Pro-apoptotic membrane receptors; death domain (DD)-containing receptors present on the cell surface such as DR4 and DR5 binds to specific pro-apoptotic ligands such as TNF related apoptosis-inducing ligand (Apo2L/ TRAIL) in order to initiate and activate the extrinsic apoptotic pathway \(^{(41)}\).

A series of cascades is activated once the receptor is bound to a specific ligand; it starts activation of the death-inducing signaling complex (DISC) through utilizing the adapter Fas-associated death domain (FADD) and procaspases 8 and 10, which result in activation of caspase cascades \(^{(42)}\).

The Apo2L/TRAIL pathway is a promising approach in cancer therapy because of its integrity in different types of cancer, induction of apoptosis in cancer cells with no effect on normal cells and irreversible to p53 function\(^{(43)}\).

Utilizing the natural ligands that selectively activate pro-apoptotic receptors such as DR4 and DR5 has been applied in the market. The synthesis of soluble recombinant human protein Apo2L/TRAIL was developed, moreover; Grenentech has developed various monoclonal antibodies that also act on pro-apoptotic receptors such as the fully human DR5 agonistic antibody Apomab\(^{(44)}\).

Recombinant human TRAIL (rhTRAIL); which known as dulanermin is TRAIL receptor agonist that showed promising activity in apoptosis induction in cancer cells \(^{(45)}\).

rhTRAIL is a soluble small protein binds to DRs with broader activity to maintain cytotoxicity but also with lack of specificity. There are numerous rhTRAIL were developed, for example: leucineisoleucine zipper TRAIL (lz-TRAIL, Iz-TRAIL), hexahistidine-TRAIL (6xHis-TRAIL), FLAG-TRAIL, and Tenascin-C TRAIL (TNC-TRAIL). They demonstrated higher stability than dulanermin but showed toxicity on normal tissue and cells \(^{(46)}\).

Another approach was obtained is the fusion of trimeric TRAIL chain to a human IgG1 crystallizable fragment (Fc) or to single-chain variable antibody fragment (scFv) which resulted in Fc-TRAILS and sc-TRAILS, respectively. This approach showed better results in apoptosis induction and stability than dulanermin \(^{(47)}\).

Wang et al., investigated the cytotoxic activity of small molecule known as biomifi or (Z)-5-(5-[(3-[4-bromophenyl]-2-imino-4-oxothiazolidin-5-ylidene) methyl] furan-2-yl) isoidoline-1,3-dione\(^{(1)}\).

Biomifi has good binding affinity to DR5 with little affinity to DR4, it showed potential cytotoxic activity on lung cancer cells H460 and H1155, the osteosarcomacellline U2OS, glioblastoma cells T98G, cervical cancer cells HeLa and colon cancer cells HT29 \(^{(48)}\).

Allen and co-workers introduced TRAIL inducing compound 10 (TIC-10); a drug was found to inhibit ERK and PI3K/Akt pathways and up regulate TRAIL receptors for apoptosis induction. This drug was also found to cross
blood brain barrier with great potential to treat central nervous system tumors \(^{(49)}\).

Various other analogues were developed such as a trifluoromethylbenzyl congener and a difluorobenzyl analogue with greater cytotoxic activity and minimal/no effect on normal cells \(^{(50)}\).

The use of ibulocydine; a synthetic drug and TRAIL mediated cell death. It is cyclin-dependent kinases inhibitor that suppresses Cdk7 and Cdk9 on cancer cells to induce apoptosis through activating caspases \(^{(51)}\).

Another study showed that 2-deoxy-D-glucose induced apoptosis through TRAIL mediated pathways in human gastric tumor cells \(^{(52)}\).

Numerous of drugs have been used before to induce the apoptotic process of DRs and ligands in the extrinsic pathway, such as cyclooxygenase-2 inhibitors, histone deacetylase (HDAC) inhibitors, proteasome inhibitors and a number of antibodies which target the DR \(^{(53)}\).

Various approaches proposed the cFLIP (cellular FLICE-like) inhibitory protein as a therapeutic target in cancer for apoptosis induction. Some studies used siRNA to inhibit the anti-apoptotic effect of cFLIP and increase the sensitivity to TRAIL-mediated pathway and/or other chemotherapeutic agents. However, these approaches showed some limitations starts from the safe delivery of the siRNA and significant homology between cFLIP and caspase-8 \(^{(54)}\).

Thus, TRAIL mediated apoptosis represent an effective approach in cancer therapy, the preclinical and clinical trials showed safety and significant effect for apoptosis induction.

**Targeting Convergence Pathway**

A merge occur between both extrinsic and intrinsic pathways of apoptosis on downstream series of caspases, it is named the execution phase which is the final pathway of apoptosis. It has been indicated that apoptosis could be suppressed at this step.

The apoptosis-inhibiting proteins (IAPs) is an evolutionarily conserved family of apoptosis suppressors, which has been shown to influence cell death \(^{(55)}\).

Poor prognosis of cancer was reported with over-expression of IAPs \(^{(56,57)}\). All IAPs family can bind and inhibit caspases family which allows them to inhibit apoptosis through the so-called BIR (baculovirus iap repeat) domain, which facilitate protein–protein interactions and prevent the conversion of inactive pro-caspases to active caspasess \(^{(58)}\).

Caspase-3 & 8 couldn't be processed and activated in response to IAPs, thereby extrinsic apoptotic signaling was inhibited \(^{(59)}\).

Several studies extensively indicated the use of IAPs in anticancer therapeutics and proved its efficiency in targeting and initiating cell suicide \(^{(60)}\).

Since their mechanism depend mainly in a balance between IAPs and their endogenous antagonists which keep them in order and promote apoptosis. Thus, the use of naturally occurring IAP-antagonists such as SMAC (Diablo) and HtrA2 (Omi) to aim and bind to IAPs in order to pave the way for caspasess to initiate apoptosis. These naturally occurring IAP-antagonists are segregated in the mitochondria and liberated to the cytoplasm during apoptosis \(^{(61)}\).

There is some cytotoxic anticancer drugs use synthetic peptidesbased that imitate the action of SMAC and HtrA2 to induce cell death or sensitize cancer cells to apoptosis \(^{(62)}\). Other IAP protein inhibitors have been developed such as: SH122, SH130, SM164, AZD5582, JP1201, AEG35156, LY2181308 and YM155 \(^{(63)}\).

**Initiating Cell Cycle Arrest to Induce Apoptosis**

One of the cancer drug target approaches has been investigated is the cyclin-dependent kinases (CDKs) family that control and monitor the cell cycle phases. For decades, CDKs was known as the main contributors of cell cycle, development, proliferation and differentiation.

However; recently, potential targets such as protein kinases that act upon DNA damage and
protein kinases that govern mitosis were identified (64, 65).

Cell cycle arrest occurs as a result of DNA lesions give the cell a chance to repair damaged DNA. The arrest of cell cycle obtained by two essential checkpoints 1 and 2 through the activation of serine–threonine protein kinase are anticipated to maintain DNA integrity and act as self-cell defenses against cancer.

There have been trials for the synthesis of kinases inhibitors as anticancer therapeutics that leads to the synthesis of BCR–ABL protein kinase inhibitor imatinib from Gleevec; Novartis, it successfully target tyrosine kinases for the treatment of chronic myelogenous leukaemia. Several studies approved that aiming CDK family members is a good addition to the list of therapeutics inducing apoptosis, particularly for CDK-2, 4 and 5. Other study suggested that CDK1 is considered a potential approach in prostate cancer, while CDK5 has a particular role in regulating cell motility and metastatic in such disease (66).

Moreover, a good understanding about the CDK family, particularly the relation between their regulators and their inhibitors have paved the ways for new strategies targeting apoptosis (64).

A study recently done by Imran Khan and colleges investigated the effect of carvacol; a flavonoid found abundantly in thyme plants. They found that carvacol efficiently cell cycle arrest by suppressing CDK-2,-4,-6, cyclin E and cyclin D1 and increasing p21 expression (67).

Zhang et al., proposed the combined use of CDK1 inhibitor RO-3306 or dinaciclib with cobimetinib (MEK inhibitor) caused cell cycle arrest and apoptosis in human colorectal cancer (68).

Humeau and co-workers investigated the role of Ca$^{2+}$ in cell cycle and cell proliferation and suggested targeting Ca$^{2+}$ as an approach for cell cycle arrest and apoptosis induction (69).

Ca$^{2+}$ is crucial for numerous physiological processes include cell differentiation, proliferation and cell death and cytoplasmic Ca$^{2+}$ levels varies along the cell cycle. Drugs targeting Ca$^{2+}$ such as Ca$^{2+}$ channel blockers can be used to target Ca$^{2+}$ channels that is over expressed in cancer, for example: T-type Ca$^{2+}$ channels, SOCE channel components (ORAI1 and STIM1), InsP3R and RyR channels, also TRPM8, TRPV6 and TRPC1/C4 channels in the TRP family (70).

**Targeting Cancer Stem Cell (CSC) to Induce Apoptosis**

Currently, there is evidence that some cancer cells have stem cell like features such as self-renewal, infinite proliferation and replication and the ability to survive toxic agents which considered is the main reason of cancer recurrence after radiation and chemotherapy (71–73) thus, the name of cancer stem cell (CSC).

Other properties of CSC include: genetic and chromosomal instability, mobilization of cellular resources, chromatin transcription, epigenetic modifications and altered environmental interactions between cancer cells and normal cells within the extracellular and endothelium (74). CSC can be originated from the transformation of normal stem cells through several genetic mutation and instability, or they can occur from tumor cells acquire stem cells like features progressively (75, 76).

Targeting and eradicating CSCs through apoptosis is a therapeutic goal for cancer and holds a promising approach to decrease morbidity and mortality in cancer patients. Therefore, many compounds have been developed to target intrinsic and extrinsic apoptotic pathways.

A combination between TRAIL and cisplatin was reported to eradicate CSCs effectively (77). For example, it showed great potentials in enhancing triple negative breast cancer stem cells death and apoptosis through suppression of Wnt signaling pathway (78). It was also reported that the co-treatment between TRAIL and cytarabine or daunorubicin inhibited the growth of progenitor cells in acute myeloid disease (79).

Moreover, when TRAIL is used in addition to Bortezomib, a proteasome inhibitor, it initiated apoptosis in glioblastoma stem cells (80). Furthermore, a study showed that injecting mesenchymal stem cells (MSC) engineered to express TRAIL into mice resulted in inhibition
of tumor growth and induction of apoptosis in squamous and lung cancer stem cell (81).

Another pathway might be initiated for the purpose of CSCs death and apoptosis is NF-kB, a transcription factor with a critical role in apoptosis signaling pathway. In fact, NF-kB suppress the programmed cell death and promotes cell proliferation, tumorigensis and metastasis (82).

Small molecules have been developed to inhibit NF-kB like parthenolide, pyrrolidinedithiocarbamate and its analog diethyldithiocarbamate. They showed a promising result in targeting breast cancer stem cells which indicate the vital activity of NF-kB to promote the proliferation cancer stem cells (83).

Other strategy occurred through the co-treatment between the proteasome inhibitor MG-132 together with the anticancer drug idarubicin induced apoptosis in leukemic stem cells through the suppression of NF-kB (84).

Recent in vivo and in vitro studies suggested the use of dietary phytochemicals to interfere in signaling transduction pathways (85-87), thus, to induce apoptosis and inhibit proliferation and cell cycle progression in tumor cells and particularly in CSCs.

Curcumin was shown to regulate miRNA expression in breast cancer stem cells, it inhibited Bcl-2 expression with the induction of apoptosis, it showed no effect on normal stem cells (88,89), curcumin in combination with resveratrol (substance found in grapes) also showed inhibition in Wnt signaling and promising targets of the self-renewal features of CSCs (90).

Isothiocyanates was reported as potent anti-cancer phytochemical. Their role depends on induction of apoptosis of CSCs and cell cycle arrest (91).

Sulforphane; a phytochemical found in broccoli was reported to target pancreatic CSCs through NF-kB (92), it was also reported to target breast cancer progenitor stem cell through Wnt/β-catenin self-renewal pathway (93). β-Carotene has been recognized to suppress the growth of CSCs in neuroblastoma (94).

A recent study by Jian-feng Li and his colleagues targeted lung cancer stem cells by the use of bispecific antibody (BsAbs) which were able to block two different antigen c-MET and CTLA-4 (95).

Their theory based upon the up regulation of Cellular mesenchymal-to-epithelial transition factor (c-MET) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) expression contributes to promoting tumorigenesis in different types of solid tumors, and targeting both antigens should suppress tumor progression through the inhibition of hepatocyte growth factor (HGF) mediated tumor development (96). HGF is cytokine present in a variety of with anti-apoptotic activities (97), thus, its inhibition would promote CSCs apoptosis.

Deregulation of PI3K/AKT/mTOR signaling is found in many cancers and the one of the reasons of treatment resistance which has a critical role in CSCs (98). The co-treatment of metformin, an anti-diabetic drug with an inhibitor of PI3K/AKT/mTOR signaling, and the RAF inhibitor sorafenib effectively reduce GSC oxidative stress and efflux pump activity, and synergistically CSCs (99). Moreover, a recent report showed that BFZ-235, an inhibitor of PI3K/AKT/mTOR signaling, effectively suppresses the stemness of colon CSCs (100).

Chao shang and his colleges suggested the role of miRNA-21 inhibition to induce glioblastoma cancer stem cells death and apoptosis through targeting FASLG as a new potential therapeutic approach (101).

Targeting miRNA to Induce Apoptosis

There is an increase attention to microRNAs (miRNAs) recently (102). They are non-coding short RNAs of 18–25 nucleotides in length. They were found to govern gene expression at post-transcriptional level, either by degradation of mRNA or stop the translation process (103). miRNAs contribute in multiple cellular functions, such as cell cycle regulation, cell differentiation, stem cell self-renewal and apoptosis.

Furthermore, it was reported that the decreased expression of miRNA causes eradication of apoptosis, which lead to carcinogenesis and resistance to the therapy (105). Therefore, restoring miRNA levels especially those
The main goal of therapeutic approaches for malignant growth depends on the way that body can maintain a healthy number of cells, yet, this concept is enormously exasperates in malignancy cells. Distinguishing proof of the key players associated with the apoptosis process and their cooperation with other members of apoptosis has supported the critical improvements made in the field of malignancy treatment.

Cancer therapy based upon initiation and induction of apoptosis has been a key methodology in battling this disease; nonetheless, we are still left with immense difficulties to be defeated.

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