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Small and Long Non-Coding RNAs: Novel Targets in Perspective Cancer Therapy

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Abstract: Non-coding RNA refers to a large group of endogenous RNA molecules that have no protein coding capacity, while having specialized cellular and molecular functions. They possess wide range of functions such as the regulation of gene transcription and translation, post-transcriptional modification, epigenetic landscape establishment, protein scaffolding and cofactors recruitments. They are further divided into small non-coding RNAs with size < 200nt (e.g. miRNA, piRNA) and long non-coding RNAs with size >= 200nt (e.g. lincRNA, NAT). Increasing evidences suggest that both non-coding RNAs groups play important roles in cancer development, progression and pathology. Clinically, non-coding RNAs aberrations show high diagnostic and prognostic values. With improved understanding of the nature and roles of non-coding RNAs, it is believed that we can develop therapeutic treatment against cancer via the modulation of these RNA molecules. Advances in nucleic acid drug technology and computational simulation prompt the development of agents to intervene the malignant effects of non-coding RNAs. In this review, we will discuss the role of non-coding RNAs in cancer, and evaluate the potential of non-coding RNA-based cancer therapies.

Keywords: Cancer, microRNA, piRNA, Long non-coding RNA, Therapeutic target, Epigenetics, RNA interference, Nucleic acid drug.

1. INTRODUCTION

Human genome undergoes pervasive transcription to generate thousands of non-coding RNA molecules (ncRNA). As revealed by ENCODE consortium, around 70% of the genome is transcribed for RNA molecules [1] that have no protein coding capacity. Instead of mere transcriptional noise, they directly function as structural, catalytic and regulatory RNAs [2-7]. NcRNAs with size smaller than 200nt are categorized into small non-coding RNA (sncRNA) which includes small interfering RNA (siRNA), microRNA (miRNA) and piwi-interacting RNA (piRNA). The rest of the ncRNA with size larger than 200nt are categorized into long non-coding RNA (lncRNA) which includes long intergenic non-coding RNA (lincRNA), natural antisense transcript (NAT), transcribed ultraconserved region (T-UCR) and non-coding pseudogene. Extensive studies are conducted to study the roles of ncRNAs in cell biology, and accumulating evidences showed that these RNA molecules play important roles in cellular functions, and their deregulation heavily contributes to various pathological conditions including cancer [8-10]. Currently, numerous sncRNAs (e.g. miR-21, miR-34a and piR-651) and lncRNAs (e.g. MALAT1 and HOTAIR) are identified to contribute the development and progression of cancer. *In vitro* data shows that targeting these ncRNAs in cancer cells can elicit effective cancer inhibitory effect. The discovery of ncRNAs' involvement in cancer prompts the development of anti-cancer treatments based on targeting these RNA molecules. As such, it is understandable that therapeutic approaches targeting aberrant ncRNAs in treating human cancers are gaining enormous momentum.

2. SMALL NON-CODING RNA

2.1. MicroRNA in Cancer

miRNAs are short, single-stranded RNA molecules that regulate gene expression at post-transcriptional and translational levels. Cellular functions of miRNAs include the regulation of proliferation, development, differentiation, and apoptosis of normal and cancer cells. They can modulate these biological processes by inhibiting critical protein factors via mRNA degradation and/or translation inhibition [2-5]. Upon processing from precursor transcripts, the mature miRNAs interact with a group argonaute-containing proteins, to form the miRNA-containing RNA induced silencing complex (miRISC). This complex functions to regulate the target translation, in which the miRNAs are responsible to the recognition of mRNA targets [2, 3]. Such targeting is based on the Watson-Crick base pairing, as the miRNAs guide the binding to a specific site at the mRNA's 3' untranslated region (3' UTR) according to sequence complementarity [2, 3]. As the binding site of each miRNA can be found in the 3' UTR of multiple mRNA, it is suggested that

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a single miRNA can regulate multiple gene targets simultaneously.

Studies show that miRNAs are aberrantly expressed in multiple cancer types, in which they heavily contribute to cancer pathology. It is observed that critical miRNAs are often up-regulated or down-regulated in cancer cells in contrast to their normal counterparts. For example, miR-21 and miR-221 is frequently up-regulated [11, 12] whereas miR-16 cluster, miR-101 and miR-145 are frequently down-regulated in multiple cancers [13]. Expression of miRNAs is also often associated with cancer signalings and pathways, as miRNAs can be activated by key oncogenic pathways. It is shown that miR-21 was transcriptionally activated by STAT3 in the interleukin 6 pathway [14], whereas expression of miR-17-93 cluster was induced by c-myc oncogene [15]. Functional studies confirmed that deregulation of miRNAs can behave as drivers for cancerous development in the same way as deregulation of protein-coding oncogenes and tumor suppressor genes. For examples, loss of let-7, an important miRNA capable of inhibiting RAS and c-myc oncogenes, effectively enhanced cellular transformation [16]. Increased miR-21 expression could suppress PTEN and PDC4 tumor suppressor genes, and promote the migration and invasion of hepatocellular carcinoma cells [17].

Cancer-associated miRNAs are generally classified into 2 groups, the oncomiRs and tumor suppressor miRNAs [8, 9]. During carcinogenesis, oncomiRs are over-expressed to deplete the tumor suppressor genes, while tumor-suppressor miRNAs are lost that leads to the accumulation of oncogenes or activation of oncogenic pathways. OncomiRs are often over-expressed in cancer. MiR-21 is an important oncomiRs that is highly up-regulated in a majority of cancer types including breast cancer [18] glioblastoma [19] liver cancer [20], lung cancer [21] and colorectal cancer [22]. Studies showed that miR-21 promotes cancer development via regulating cell transformation, proliferation, cell cycle, apoptosis and metastasis [20, 23-25]. On the other hand, tumor suppressor miRNA functions to prevent malignant development of cells. In cancer, the levels of tumor suppressor miRNAs are often reduced. MiR-34a is one of the critical tumor suppressor miRNAs, and its expression is lost in multiple cancers such as colorectal cancer [26], prostate cancer [27], liver cancer [28], glioblastoma [29], lung cancer [30] and bladder cancer [31]. miR-34a is the direct transactivation target of p53 for the induction of apoptosis and cell cycle arrest [32, 33]. Gene targets of miR-34a often promote carcinogenesis. Direct target of miR-34a includes Notch, Bcl-2, c-Myc, E2F3, c-Met and SIRT [34]. Accumulating evidences suggested that reversal of the aberrant miRNA levels can induce significant anti-cancer effects.

2.2. Piwi-interacting RNA (piRNA) in Cancer

piRNA is a new class of ncRNA known to form complex with PIWI-specific Argonaute proteins [35-37]. Currently, piRNAs are identified as the largest class of sncRNA, with 24–32 nucleotides in length. piRNAs interact with Piwi complex to form functional RNA-protein complex. Piwi group protein is evolutionally conserved and regulates the maintenance and self-renewal of germline stem-cell [38]. One of the major functions of Piwi-piRNA pathway is the silencing of transposon. The regulation of transposon by piRNAs allows the development and maintenance of DNA integrity [39]. In addition, it is believed that piRNAs are involved in gene regulating epigenetically. piRNAs are critical in determining the co-localization of Piwi and epigenetic factors HP1a, Su(var)3-9 and Polycomb group proteins [40]. Loss of Piwi resulted in a reduction of histone 3 lysine 9 methylation, and an elevation of polymerase II occupancy that led to the reactivation of transcript expression [41, 42]

There are reports suggesting that piRNA-Piwi pathway may have a role in cancer biology. Human Piwi proteins, HIWI and HILI, are aberrantly expressed in a variety of cancers. The level of HIWI is aberrantly altered in testicular germ-cell tumor, gastric cancer, soft-tissue sarcoma and pancreatic ductal adenocarcinoma [43-45]. The expression of HIWI was associated with the proliferation of human gastric cancer cells [45]. Moreover, in patients suffering with pancreatic ductal adenocarcinoma and soft-tissue sarcoma, high Hiwi mRNA levels were associated with poor patients' survival [44]. HILI, another human homolog of Piwi, is also shown to express in breast cancer [46], colon cancer [47] and cervical cancer [48].

Recently, piRNAs that are associated with cancer pathology have been identified. piRABC was highly down-regulated in bladder cancer tissues compared to their adjacent normal tissues [49]. piR-651 was up-regulated in gastric, colon, lung and breast cancer tissues, that played a role in cancer cell proliferation [50]. Over-expression of piRABC could inhibit bladder cancer cell proliferation, colony formation, and promote cell apoptosis. piRABC could regulate target gene transcriptionally, as it increased the promoter activity of TNFSF4 gene [49]. piRNA-823 was another cancer-associated piRNA. The level of this piRNA was reduced in gastric cancer tissues compared to non-cancerous tissues. Upon over-expression of piRNA-823, gastric cancer cell growth and tumor growth were inhibited [51]. However, the role of piRNA-823 during cancer development is ambiguous. In another report, the level of piRNA-823 was increased in multiple myeloma patients and cell lines. piRNA-823 level is positively correlated with clinical stage of the patients [52]. Knockdown of piRNA-823 inhibited the tumorigenicity both *in vitro* and *in vivo* through the alteration of cell cycle and apoptotic pathway. In addition, inhibition of piRNA-823 in multiple myeloma cells reduced vascular endothelial growth factor secretion, leading to a decrease of proangiogenic activity [52]. Therefore, careful examination is necessary to determine the putative role of piRNAs in cancer.

2.3. Targeting Small ncRNA in Cancer Therapy

After we observe how the expression of a specific sncRNA is altered, we can reverse the alteration to restore their normal physiological functions in cancer cells. In general, the use of antagonists and mimics are two approaches to achieve sncRNA-based therapeutics. Antagonists are reported to inhibit endogenous miRNAs or piRNAs that show tumor promoting functions in cancer cells or tissues. It involves the introduction of a RNA oligonucleotide complementary to the target miRNAs or piRNAs. It is shown that the antagonist of miR-21 could reverse epithelial to mesenchymal transition and cancer stemness in breast cancer [53].

The strand is usually modified chemically to bind to the target miRNAs with high affinity. The activity of target miRNA is hampered because the new miRNA duplex is unable to incorporate into the RISC complex due to high RNA duplex stability. In addition, the miRNA duplex can be subjected to degradation, resulting in a reduced miRNA activity. Antagonist can also be used to inhibit piRNAs. The use of piR-651 antagonist could inhibit cell growth by inducing G_2/M phase arrest [50]. On the other hand, we can reverse the loss of sncRNAs by using RNA mimics to restore the tumor suppressing effects. This is accomplished by introducing the RNA duplex, which has one strand resembling the sequence of the targets, into cancer cells with suboptimum level of the tumor suppressor sncRNA. For example, treatment of mimics of miR-218 could inhibit both cell growth and tumor growth in pancreatic ductal adenocarcinoma cells [54]. In addition, mimic of piRNA piR_015520 was proved to be capable of repressing its target gene MTNR1A expression [55]. As such, therapeutic effects are delivered as pathways are reactivated to trigger effects unfavorable to cancer cells.

Modulation of miRNA level is not limited to nucleic acid approach. Recently, different groups have developed small molecules to either inhibit or induce the expression of specific miRNAs in cancer cells. Small molecule inhibitor of miR-21 could block the biogenesis of mature miR-21 from pre-miR-21 by attenuating Dicer cleavage [56]. This inhibitor could suppress tumor growth and invasion via the upregulation of miR-21 functional targets such as PTEN [19]. miR-21 inhibitor treatment could also induce the reversal of epithelial-mesenchymal transition in epithelial tumor cells and orthotopic nude mouse model [56]. Other than miR-21, the level of miR-122 can also be modified by small molecules. Both inhibitors and activators were generated that are capable of inducing the downregulation or upregulation of miR-122 transcriptionally [57]. Study showed that inhibitor of miR-122 could inhibit HCV replication in liver cells, as it is a critical component for hepatitis C virus replication. Moreover, activator of miR-122 could elicit proapoptotic effect in cancer cells. This small molecule could up-regulate miR-122 in the hepatocellular carcinoma cells, and subsequently increased caspase expression, leading to cell apoptosis and reduced cell viability [57]. Another miRNA activator was discovered to up-regulate a tumor suppressor miRNA miR-34a expression. A natural product Rubone was screened out that was capable of transcriptionally upregulating miR-34a level in hepatocellular carcinoma cells [58]. The study showed that Rubone could increase miR-34a promoter activities and p53 occupancy on miR-34a promoter in both wildtype and mutant p53. Through the modulation of miR-34a level, Rubone could significantly inhibit hepatocellular carcinoma cell growth and tumor growth without showing toxicity to non-tumor hepatocytes [58].

Biogenesis of mature miRNA provides another avenue for modulating miRNA level. Inhibition of miRNAs can be achieved by interfering the maturation of the precursor molecules of miRNA. Aptamer, a stable 3-dimensional structure formed by DNA or RNA oligonucleotides or peptides, is one of the agents that can serve this purpose. Aptamers can interact with a broad range of molecules such as protein, RNA, and small molecules with high specificity. The binding relies on the structural interaction of the aptamer with the 3-dimensional shape of the targets [59]. Study showed that aptamer interfered the maturation of miRNAs by targeting the apical loop domain of pri-microRNA molecules, subsequently leading to the depletion of miRNAs. A previous report showed that an aptamer was screened out that could selectively interact with the target pri-miR-18a, and inhibit the binding of hnRNP A1 to the apical loop of pri-microRNA which subsequently interrupted miR-18a maturation [60]. Another aptamer was developed that could abrogate the biogenesis of miRNAs at the entire miR-17-92 cluster. Treatment of miR-17-92 aptamer could block the biogenesis of mature miR-17, miR-18a and miR-19b in retinoblastoma cell lines, leading to cell cycle arrest and apoptosis [61].

In addition to being the drug targets, miRNAs can be regarded as the drug used in cancer treatment. Ectopically introducing miRNAs that repress the level of oncogenic protein coding mRNAs is another potential therapeutic strategy against cancers. Like siRNAs, mimics of miRNA can be employed as therapeutic agents to target specific oncogene or oncogenic network based on its endogenous gene silencing ability of miRNAs. In this way, instead of reversing the loss of miRNAs, the aim of the miRNAs introduction is to induce gain of functions in cancer cells that elicits tumor suppressing effects. Such idea has been verified by the study in which the level of oncogene BCR/ABL was suppressed by an array of synthetic miRNAs [62]. miRNA-based agents is suitable for pharmaceutical drug development because report shows that they do not induce adverse effect in normal tissues. Taken together, treatment with ectopic miRNA is a promising regime.

3. LONG NON-CODING RNA (LncRNA)

3.1. LncRNA in Cancer

GENCODE project has annotated 14,880 lncRNAs from 9277 loci [63]. Studies demonstrate that lncRNAs are involved in a variety of biological roles including embryogenesis [64], stem cell biology and cellular development [65], apoptosis and cell cycle control [66]. LncRNAs contribute in various molecular roles including imprinting [67], epigenetic regulation [68], transcriptional [69] and translational regulation, splicing, cell development and differentiation [70]. Although only a small proportion of lncRNAs are characterized, several studies have identified a few lncRNAs that have important roles in cancer pathology [66]. Metastasis Associated Lung Adenocarcinoma Transcript 1 (MALAT1) is a lincRNA functions to regulate gene expression and post-transcriptional modification [71]. It belongs to one of the lncRNAs that contributes to cancer development and progression. MALAT1 promoted cell growth, cell cycle progression and invasion in hepatocellular carcinoma and bladder cancer [72-74]. Another critical cancer-associated lincRNA is HOX Transcript Antisense Intergenic RNA (HOTAIR). It acts as a scaffold to recruit both PRC2 and LSD1 histone modifying complexes [75, 76]. HOTAIR functions to suppress gene expression by bringing the histone modifying complexes to target gene promoter for establishing suppressive histone methylation. High level of HOTAIR

can be detected in various kind of cancers including breast cancer [76], colon cancer [77], liver cancer [78], gastrointestinal stromal cancer [79] and pancreatic cancer [80]. Reports showed that high HOTAIR level was associated with poor patient prognosis [77, 80, 81].

Expression of lncRNAs is specific to tissue types and developmental status [82, 83]. As such, treatment developed based on these lncRNAs can provide better selectivity. Highly Up-regulated in Liver Cancer (HULC) has strikingly high specificity to liver cancer. The lncRNA harbors miRNA-binding regions to sequester miRNAs, regulating activity of the miRNAs [84]. HULC was specifically upregulated in hepatocellular carcinoma tissues and metastatic tissues developed in liver [85, 86]. In addition, level of HBx protein, a HCC-related viral protein, was highly associated with that of HULC [87]. These evidences indicate the high specificity of HULC expression in primary or secondary tumors grown in liver. Another lncRNA that shows great tissue specificity is Prostate Cancer Gene Expression Marker 1 (PCGEM1) which can only be detected in prostate tissue [88]. One of the reasons for the high specificity of PCGEM1 to prostate cancer is owing to its dependency on androgen. [88]. PCGEM1 plays important roles in prostate cancer development [88, 89]. High PCGEM1 level was observed in prostrate tumors compared to correspoding non-tumor tissues [90]. Study showed that PCGEM1 served as coactivator of androgen receptor and c-Myc that reprogrammed the transcriptional network metabolic genes and androgen-responsive genes [91]. The oncogenic role of PCGEM1 has been shown as studies demonstrated that overexpressing PCGEM1 could promote cell growth and colony formation in prostate cancer cells and mouse epithelial cell line.

Other lncRNA groups also contribute to cancer development or progression. It is found that the NAT of INK4b-ARF-INK4a gene cluster, Antisense Non-coding RNA in the INK4 Locus (ANRIL), coordinated with polycomb complexes for the silencing of genes within the cluster including p14, p15 and p16. ANRIL was over-expressed in prostate cancer, and its level was negatively correlated with p16 level in preneoplastic and neoplastic prostate epithelial tissues [92]. INK4b-ARF-INK4a gene cluster regulates cell-cycle, senescence and stress-induced apoptosis, while the major function of ANRIL is to repress this gene cluster [93-95]. In addition to NAT, profiling of transcribed ultraconserved region (T-UCR) identified T-UCR uc.279 and uc.460 that were up-regulated in neuroblastoma with MYCN amplification. As MYCN amplification is strongly associated with neuroblastoma aggressiveness, these T-UCRs may contribute to neuroblastoma progression as MYCN downstream effectors. Indeed, their levels showed association with both the clinical and genetic features of neuroblastoma [96]. Furthermore, Oct4-pg is a non-coding pseudogene that acts as a decoy of its corresponding gene to sequester Oct4 targeting miRNAs. Oct4-pg potentially regulates cell stemness and pluripotency, and this non-coding pseudogene is capable of regulating OCT4 gene activity. In hepatocellular carcinoma, high OCT4-pg level was associated with elevated OCT4 expression. Oct4-pg was also detected in numerous cancer cell lines and tissues of diverse cell origins [97].

3.2. Targeting lncRNA in Cancer Therapy

Therapeutic strategies target lncRNAs mainly through depleting the oncogenic lncRNAs in cancer cells (98). Currently, nucleic acid-based methods are the most popular approaches to target RNA molecules, and they are able to regulate the level of lncRNAs, modify their structures or block their functional motifs. RNA interference (RNAi)-based techniques are extensively used to inhibit lncRNAs in cancer cells. This technique employs short stretched (19-30 nt) of double-stranded RNA, such as small interfering RNA (siRNA), that determines the target specificity in the RNAi pathway. Inhibition of lncRNAs is achieved as the double stranded RNA elicits a RISC-mediated degradation of target lncRNA molecules. As such, oncogenic lncRNAs could be depleted in cancer cells, which leads to the induction of anti-cancer effects. For instances, siRNAs targeting HOTAIR RNA inhibited cell invasion ability of breast cancer cells [76], and xenograft growth of pancreatic cancer cells [80]. siRNAs targeting HULC and MALAT1 decreased cell proliferation rate [87] and halted cell cycle progression [99] of hepatocellular carcinoma cells.

Other than RNAi-based technique, lncRNAs can be inhibited by simple nucleic acid duplex formation. It is achieved by the use of antisense oligonucleotides (ASOs) which are short, single stranded DNAs or RNAs having the size between 8 to 50 nucleotides. The sequence of the ASO is antisense to its target RNA that allows the specific binding for target degradation. ASO is a promising agent to target lncRNAs during cancer treatment. A study used ASO to abrogate the post-transcriptional modification ability of MALAT1 [71, 100]. Inhibition of MALAT1 by ASO induced cell cycle arrest specifically to cancer cells [100]. ASO targeting MALAT1 inhibited *in vivo* tumor growth and metastasis of lung cancer cells [99]. Another ASO was designed to deplete the NAT of BDNF. Such inhibition attenuated the inhibition function of the NAT to its corresponding gene BDNF expression [101]. Another RNAi-independent method involved the use of hammerhead ribozyme (HamRz), a member of catalytic RNA enzyme. HamRz RNA is fold into a structure that is consisted of two unpaired binding arms. Upon the binding between its binding arms and its lncRNA targets, HamRz catalyzes their degradation by destabilizing their phosphodiester backbone [102, 103]. The anticancer potential of HamRz has been demonstrated as the inhibition of VEGFR mRNA by HamRz could reduce colorectal cancer growth and metastasis *in vivo* [104]. Theoretically, HamRzs show higher specificity to its target than siRNA and ASO, as perfect matching to the two non-contiguous binding arms of the HamRz is required for the folding of catalytic core. The cleavage of the targets is carried out only when the catalytic structure is formed. In addition, the cleavage activity of HamRz is independent of any cell component. Superior to RNAi, it will not elicit unspecific effect due to saturation of any cellular machinery.

The above methods based on the Watson-Crick base pairing ability of the nucleic acid-based drug. Inhibitory effect to the lncRNA can be independent of the sequence complementarity. Aptamers can be used to modulate lncRNA through structural interaction. Aptamer shows higher RNA secondary structure binding specificity and affinity compared to an-

tisense oligonucleotides [105]. Aptamers show therapeutic potential via targeting lncRNAs as they are capable of degrading RNA or inhibiting RNA functions. A hairpin aptamer is generated to inhibit TAR-dependent viral protein expression via specifically interacting with the TAR RNA element of HIV-1 mRNA [106]. Another aptamer is screened out to regulate TAR-mediated process through the formation of stable loop-loop complexes with TAR element [107]. Other than aptamer, small molecules can also potentially modulate lncRNAs. A research group developed a short string of nucleotides and peptide/small molecules hybrids to target a CUG-repeat mRNA mutant with high selectivity. The molecule hybrids could effectively reduce the myotonic dystrophy type 1 symptoms in mice [108]. Polymerized bisbenzimidazole Hoeschst 33258 is another compound that could interact with CUG-repeat mRNA. It could inhibit the CUG-repeat mRNA/MBNL1 in both myotonic dystrophy type 1 and spinocerebellar ataxia type 3 [109]. Small molecules are also employed to inhibit HCV virus. A benzimidazole derivative is identified that could alter the subdomain hairpin loop structure of HCV RNA IRES. As such, replication of the virus was disrupted as the IRES failed to interact correctly with ribosome, leading to the inhibition of viral protein translation from host cells [110].

4. CONCLUSION

Vast amount of preclinical data suggest that modulation of ncRNAs is able to elicit significant anti-cancer effects. The improvement of nucleic acid modulating agents and drug design pipeline allows the generation of effective ncRNA targeting drugs. As such, there is a huge expectation that cancer therapeutic treatment based on targeting of ncRNAs will be promptly developed. Practically, the development of ncRNA-based therapy is still in infancy, and there are several issues awaited to be addressed. For miRNAs, extensive studies have been conducted to identify critical miRNAs in different cancer types. The roles of these miRNAs have been clearly determined and rigorously verified. However, the functions and roles of piRNAs and lncRNAs are largely unexplored. Their putative functions and roles in cancer require further verification. Secondly, efficient delivery remains one of the crucial issues for effective therapy. Nucleic acid-based drugs are still the preferable agents in targeting ncRNAs, but they are generally poor in accessibility into cancer cells. Also, it is shown that most lncRNAs functions in nucleus for epigenetic regulation [63]. Hence, there is a need to improve the current drug delivery methods to allow effective targeting of these nuclei-bound lncRNAs. Moreover, the specificity of the drugs to the cancerous cell population also requires further improvement. Given the significant inhibitory effect brought out by targeting ncRNAs in cancer, it is foreseeable that the researches on ncRNA-based therapies are gaining greater interest in the future.

LIST OF ABBREVIATIONS

3’ UTR = -3’ untranslated region

ANRIL = Antisense Non-coding RNA in the INK4 Locus

ASO = Antisense oligonucleotide

HamRz = Hammerhead ribozyme

HOTAIR = HOX Transcript Antisense Intergenic RNA

HULC = Highly Up-regulated in Liver Cancer

LincRNA = Long intergenic non-coding RNA

LncRNA = Long non-coding RNA

MALAT1 = Metastasis Associated Lung Adenocarcinoma Transcript 1

miRISC = MicroRNA-programmed RNA induced silencing complex

miRNA = MicroRNA

NAT = Natural antisense

ncRNA = Non-coding RNA

PCGEM1 = Prostate Cancer Gene Expression Marker 1

piRNA = Piwi-interacting RNA

RNAi = RNA interference

siRNA = Small interfering RNA

sncRNA = Small non-coding RNA

T-UCR = Transcribed ultraconserved region

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflict of interest.

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