Noncoding RNAs in Prostate Cancer: The Long and the Short of It

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Abstract

As the leading culprit in cancer incidence for American men, prostate cancer continues to pose significant diagnostic, prognostic, and therapeutic tribulations for clinicians. The vast spectrum of disease behavior warrants better molecular classification to facilitate the development of more robust biomarkers that can identify the more aggressive and clinically significant tumor subtypes that require treatment. The untranslated portion of the human transcriptome, namely noncoding RNAs (ncRNA), is emerging as a key player in cancer initiation and progression and boasts many attractive features for both biomarker and therapeutic research. Genetic linkage studies show that many ncRNAs are located in cancer-associated genomic regions that are frequently deleted or amplified in prostate cancer, whereas aberrant ncRNA expression patterns have well-established links with prostate tumor cell proliferation and survival. The dysregulation of pathways controlled by ncRNAs results in a cascade of multicellular events leading to carcinogenesis and tumor progression. The characterization of RNA species, their functions, and their clinical applicability is a major area of biologic and clinical importance. This review summarizes the growing body of evidence, supporting a pivotal role for ncRNAs in the pathogenesis of prostate cancer. We highlight the most promising ncRNA biomarkers for detection and risk stratification and present the state-of-play for RNA-based personalized medicine in treating the "untreatable" prostate tumors.

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No potential conflicts of interest were disclosed.

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Learning Objective(s)

Upon completion of this article, the reader should have a good understanding of the major small and long noncoding RNAs involved in prostate carcinogenesis, their potential as biomarkers, and the biologic rationale underlying novel therapeutic strategies using noncoding RNAs for castration-resistant prostate cancer.

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Introduction

It was somewhat humbling to learn that the human genome encodes only 20,000 or so protein-coding genes, in the same region as the worm or mouse. Was it really true that >90% of our DNA were so-called "junk," lying idle? In 2007, it transpired that in fact most of our DNA is transcribed into biologically crucial regulatory molecules, branded noncoding RNAs (ncRNA; refs. 1 and 2). Noncoding because they are not translated into conventionally purposeful protein end-products, but nevertheless, these molecules, both long and short, little and large have emerged as vital parts in our complexity. They are key factors in maintaining normal cellular function and therefore play an enormous role in human disease, including cancer. So what exactly do ncRNAs do? Broadly speaking, ncRNAs can be divided up into those with “housekeeping” functions such as mRNA processing and protein synthesis and those exhibiting cell-type-specific expression and more “regulatory functions” such as pre- and posttranscriptional...
gene regulation and chromatin assembly. The rapid development of RNA microarrays and next-generation sequencing of transcriptomes (RNA-Seq) has resulted in an unparalleled treasure-trove of data on gene expression, structural rearrangements (i.e., gene fusions, copy number alterations, and alternatively spliced forms), and detection of undiscovered transcripts such as chimeric RNAs (3). Cumulative evidence from these studies supports a significant role for the untranslated, noncoding portion of the human genome in cancer initiation, development, and progression.

Responsible for approximately 30,000 deaths annually in the United States and 258,000 deaths worldwide, prostate cancer is the most common noncutaneous malignancy and third leading cause of cancer-related deaths in men in the Western world (4). This review provides a snapshot of the variety of roles ncRNAs play in prostate carcinogenesis. We also highlight the significant contributions these molecules can make as prostate cancer biomarkers and their potential therapeutic implications.

Small ncRNAs in prostate carcinogenesis
The human genome includes a diverse collection of ncRNAs, which can be broadly grouped according to size and function (Table 1). Noncoding transcripts originate from intergenic sequences, introns of “host” protein-coding genes, or antisense strands. Small ncRNAs (<200 nucleotides) participate in a variety of cellular functions.

**microRNAs**
Without a doubt, microRNAs (miRNA) remain the best-characterized class of small ncRNAs, with 2,578 mature human transcripts listed in miRBase v20 (5). It is estimated that up to 60% of human transcripts are regulated by miRNAs (6). Many excellent reviews have recently summarized the biogenesis of miRNAs and their role in human disease and cancer (7–9). In prostate cancer, several groups have conducted miRNA expression profiling studies using a range of different platforms (10–15). A common finding is that miRNAs tend to be preferentially downregulated during prostate cancer progression and metastatic spread.

**Table 1. Functional classification of major human genomic ncRNAs**

<table>
<thead>
<tr>
<th>RNA type</th>
<th>Symbol</th>
<th>Length (nt)</th>
<th>Function</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Translation and protein synthesis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ribosomal RNA</td>
<td>rRNA</td>
<td>121–507</td>
<td>Facilitates passage of tRNAs along the mRNA during translation</td>
<td>4 genes present in hundreds of copies</td>
</tr>
<tr>
<td>Transfer RNA</td>
<td>tRNA</td>
<td>73–94</td>
<td>RNA adaptor molecule that physically links the mRNA nucleic acid sequence with the peptide amino acid sequence at the ribosome</td>
<td>~500</td>
</tr>
<tr>
<td>Ribonuclease P</td>
<td>RPPH1</td>
<td>341</td>
<td>RNA component of ribonuclease P, involved in tRNA maturation and RNA polymerase III transcription</td>
<td>1</td>
</tr>
<tr>
<td>Telomerase RNA</td>
<td>TERC</td>
<td>451</td>
<td>RNA component of telomerase that provides the template for de novo synthesis of telomeric DNA</td>
<td>1</td>
</tr>
<tr>
<td>Regulatory RNAs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>miRNA</td>
<td>miR</td>
<td>~22</td>
<td>Negatively regulate gene expression posttranscriptionally through base pairing to the 3'-UTR of target mRNAs and inhibiting protein translation and/or mRNA degradation</td>
<td>~2,578</td>
</tr>
<tr>
<td>Piwi-interacting RNA</td>
<td>piRNA</td>
<td>25–33</td>
<td>Silence transposons during spermatogenesis</td>
<td>~23,000</td>
</tr>
<tr>
<td>Long noncoding RNA or</td>
<td>IncRNA</td>
<td>&gt;200</td>
<td>Various</td>
<td>Unknown, estimated at ~20,000</td>
</tr>
<tr>
<td>Small intergenic noncoding RNA</td>
<td>LincRNA</td>
<td>~150</td>
<td>Assemble around newly transcribed pre-mRNA in the spliceosome to remove introns during mRNA processing</td>
<td>~9</td>
</tr>
<tr>
<td>Small nuclear RNA</td>
<td>snRNA</td>
<td>70–200</td>
<td>Guide chemical modifications (methylation and pseudouridylation) of other ncRNAs (tRNA, tRNA, sRNA); alternative splicing in cis and trans gene regulation; may also function as miRNA</td>
<td>~200, some present in several copies</td>
</tr>
</tbody>
</table>
However, this finding could be unduly influenced by differences in sample tissue composition and a reduction in the stromal contribution in advanced and metastatic prostate cancer, rather than true biologic meaning. Most recently, a profiling study by Liu and colleagues examined miRNA expression across 6 prostate cancer stem/progenitor cell populations and proposed that a distinct set of miRNAs (downregulation of miR-34a, let-7b, miR-106a, and miR-141 and upregulation of miR-301 and miR-452) coordinate regulate prostate cancer stem cells (16). Of primary interest in this review are those miRNAs experimentally proven to be directly involved in prostate cancer development and progression.

Prostate epithelial cells require androgens and androgen receptor signaling for their proliferation and survival and as such hormone deprivation by chemical castration is the first-line therapeutic modality for patients with advanced disease. Favorable responses are short-lived and progression to lethal castration-resistant prostate cancer (CRPC) is inevitable. The androgen receptor is expressed throughout prostate cancer progression and its overexpression at both gene and protein level is a consistent feature of CRPC, where its activity as a transcriptional activator has been shown to induce a distinct set of mitotic cell cycle genes resulting in androgen-independent growth (17). A gain-of-function analysis of 1,129 miRNAs combined with androgen receptor protein quantification by reverse-phase protein lysate microarray and 3′-UTR luciferase reporter assays in a panel of prostate cancer cell lines identified 13 miRNAs that target AR mRNA (miR-135b, miR-185, miR-297, miR-299-3p, miR-34a, miR-34c, miR-371-3p, miR-421, miR-449a, miR-449b, miR-634, miR-654-5p, and miR-9): several of these also inhibited androgen-induced proliferation. Analysis in clinical specimens confirmed a negative correlation with miR-34a and miR-34c expression and androgen receptor levels (18). The members of the miR-34 family are regulated by transcription factor P53 and have been suggested to be potent mediators of tumor suppression by P53, implicated in the negative control of the cell cycle, senescence, and apoptosis (19, 20). miR-34c was previously found to be significantly downregulated in prostate tumors and linked with disease aggressiveness (21). In addition to the AR, MYC, and cell adhesion and stem cell marker CD44 have been identified and validated as direct and functional targets of miR-34a (22, 23). miR-34-a is underexpressed in CD44+ prostate cancer cells from both xenografts and primary tumors. Enforced expression of miR-34a inhibited clonogenic expansion, tumor regeneration, and metastasis, whereas delivery of miR-34a antagonirs in CD44+ prostate cancer cells promoted tumor development and metastasis. This would suggest that miR-34a negatively regulates the tumor initiating capacity of prostate cancer stem cells (23). miR-205 is possibly the best-characterized tumor suppressor miRNA in prostate cancer. Hypermethylation of the MIR-205 locus is associated with a decrease in miR-205 expression in prostate cancer cell line LNCaP (40-fold induction upon 5-aza-CdR treatment) and localized prostate cancer compared with matched histologically benign prostate tissue (24). MIR-205 hypermethylation was also shown to be a significant predictor of biochemical recurrence (24). Argonaute-2 co-immunoprecipitation experiments revealed that miR-205 targets mRNAs involved in mitogen-activated protein kinase and androgen receptor signaling pathways, including the AR itself (25, 26). miR-205 also plays an important role in counteracting epithelial-to-mesenchymal transition (EMT) and reducing cell migration and invasion by inactivating EMT regulators ZEB1 and ZEB2, which downregulate epithelial marker e-cadherin and upregulate mesenchymal marker vimentin (27, 28). It was recently shown that metastasis suppressor P63 mediates its repressive effects on cell migration and EMT marker ZEB1 through transcriptional activation of MIR-205 in the PC3 cell line (29, 30).

Allelic loss of the MIR-15A-MIR-16-1 cluster on chromosome 13 is correlated with progression of prostate cancer from early stage to metastatic disease. Antagonirs designed to specifically sequester and inhibit miR-15a and miR-16 activity resulted in increased proliferation, migration, and survival in nontumorigenic prostate cells in vitro and in vivo. Furthermore, restoration of miR-15a and miR-16 expression in LNCaP prostate cancer cells resulted in growth arrest and apoptosis. Luciferase assays showed a direct interaction between both miRs and CCND1, WNT3A, and BCL2 transcripts, indicating that this miRNA cluster contributes to prostate carcinogenesis by targeting multiple oncogenic pathways, namely cell-cycle progression, Wnt signaling, and apoptotic resistance (31). A number of studies have focused on miRNAs involved in the transformation of hormone-sensitive prostate cancer to the lethal castration-resistant phenotype. miRNA expression profiling in androgen-dependent LNCaP cell line and LNCaP-derived androgen-independent LNCaP-Abl cell line identified miR-221 and miR-222 as the most strongly upregulated miRNAs in LNCaP-Abl (10.8- and 6.5-fold, respectively, P < 0.001; ref. 32). Analysis in clinical specimens revealed that overexpression of miR-221/222 in bone metastatic CRPC relative to normal prostate tissue was highly significant (P < 0.001; ref. 33). Functional investigations using LNCaP cells showed that overexpression of miR-221/222 reduced dihydrotestosterone-induced growth and expression of certain androgen receptor–responsive genes [including prostate-specific antigen (PSA)] and resulted in androgen-independent growth (32, 34). miR-221 and miR-222 are upregulated in several cancer types and many different targets have been proposed. However, these transcripts were found to be irrelevant in CRPC and two new potential targets of miR-221 were identified: HECTD2 and RAB1A, although the mechanisms by which they mediate the miR-221/222–induced CRPC phenotype remain to be deciphered (34).

Other small ncRNAs

Studies addressing the expression and functional role of other small ncRNAs (Table 1) in prostate cancer are surprisingly lacking. Deep sequencing of the entire small transcriptome in organ-confined and metastatic lymph
node prostate cancer revealed that the total count and diversity of tRNAs and snoRNAs increased by >20% during tumor metastasis (15). The authors hypothesized that this was indicative of the high metabolic activity and elevated protein synthesis of advanced tumors. The snoRNA gene U50 has been proposed as a tumor suppressor; located within 6q14-15 (commonly deleted in multiple human cancers), it displays a homozygous 2-bp deletion detected in approximately 10% of prostate tumors, which was significantly associated with clinically significant disease (35).

**Long ncRNAs in prostate carcinogenesis**

Human long ncRNAs (IncRNAs, >200 nucleotides) are structurally similar to protein-coding genes. They contain proximal promoter sequences and consist of exons and intervening introns but possess no open reading frames. Their biogenesis is also similar to that of mRNAs; they are transcribed by RNA polymerase II and then spliced, polyadenylated, and 5'-capped. Yet, they exhibit both nuclear and cytoplasmic localization (Fig. 1). Although IncRNAs constitute the majority of the transcriptome, we certainly understand less of their biologic functions than those of their small counterparts (Table 1; ref. 36). They are attributed with an ever-increasing number of functional activities including genomic imprinting and both cis- and trans-acting transcriptional regulation. This is achieved via a variety of mechanisms such as natural antisense inhibition of contiguous genes, transcriptional interference, recruitment of chromatin remodeling complexes to specific gene loci, and promoter inactivation by binding to basal transcription factors (36–39).

One of the earliest IncRNAs described in prostate cancer was prostate cancer gene expression marker 1 (PCGEM1), a prostate-specific transcript encoded on 2q32 (40). It promotes cell proliferation and inhibits apoptosis in vitro, although the molecular mechanisms behind this remain to be elucidated (41, 42). PCGEM1 has also been hypothesized to contribute to ethnic variation in prostate cancer incidence (41).

In the most comprehensive analysis of IncRNAs in prostate carcinogenesis to date, Prensner and colleagues analyzed the transcriptomes of 102 prostate tumors and cell lines by RNA-Seq (43). The authors reported 121 long intergenic ncRNAs (lincRNA), whose expression patterns distinguished benign, localized, and metastatic cancers. They described prostate cancer–associated transcript 1 (PCAT1), a novel prostate cancer lincRNA on 8q24, in the locality of well-characterized prostate cancer risk-related single-nucleotide polymorphisms (SNP) and the c-MYC oncogene (44). PCAT1 was found to be upregulated in a subset of metastatic and high-grade localized tumors and to promote cell proliferation in vitro through transcriptional regulation of target genes. PCAT1 and EZH2 expression were shown to be mutually exclusive and knockdown or inhibition of EZH2 caused reexpression of PCAT1 and downregulation of its target genes (43).

That same year, Chung and colleagues reported prostate cancer susceptibility SNPs within a 13-kb intron less linRNA also on 8q24, which they termed prostate cancer noncoding RNA 1 (PRNCR1; ref. 45). PRNCR1 was found to be upregulated in a small sample set of precursor prostate intraepithelial neoplasia and prostate tumors. siRNA-mediated transfer of miRNA
mediated knockdown of PRNCR1 reduced cell viability and transactivation by the androgen receptor, although the precise mechanisms behind these observations were not elucidated. Fascinatingly, a search on the UCSC Human Genome Browser (Feb 2009 assembly) reveals that PCA3 and PRNCR1 are adjoining neighbors on 8q24, separated by only 60 kb of DNA desert (46). Other SNP analyses with respect to prostate cancer risk-related loci have revealed an enrichment in IncRNA sequences and also identified new risk-related loci, such as 19p13 (47).

A handful of other IncRNAs have also been associated with prostate cancer. A small RNA-Seq study on 14 Chinese prostate tumors and adjacent benign tissues identified 137 IncRNAs that were significantly altered (48). The CDKN2A–CDKN2B tumor suppressor locus is subject to frequent deletion and hypermethylation in cancers, including prostate cancer. ANRIL is an antisense IncRNA elevated in prostate cancer that overlaps this locus, interacting directly with polycomb repressive complex 1 and histone H3K27 methylation to repress CDKN2A–CDKN2B expression (49).

Providing a link between ncRNAs and chromosome structure is telomerase, a ribonucleoprotein polymerase responsible for the synthesis of the tandem hexameric repeat sequence (TTAGGG) at chromosome termini. Telomerase activation and subsequent maintenance of telomeres are required for tumor cell survival and proliferation. The telomerase core enzyme consists of an RNA component (TERC) that provides the template for de novo synthesis of telomeric DNA, and a protein catalytic subunit (TERT) with reverse transcriptase activity. TERC is expressed in all human tissues regardless of telomerase activity, whereas TERT is overexpressed in >90% of tumor cells. Antisense oligonucleotide–mediated knockdown of TERC significantly reduced cell viability in PC3 and DU145 cell lines and reduced tumor growth in nude mice via induction of apoptosis (50), although this effect was not seen by others (51). Amplification of the TERC gene has been reported in 5% of hormone-naïve prostate tumors and in approximately 16% of CRPC (52). In support of this, in situ hybridization for TERC showed upregulation in luminal epithelial cells during malignant transformation of the prostate, although a high degree of heterogeneity was observed in neoplastic cells (53).

ncRNAs as diagnostic and prognostic biomarkers for prostate cancer

Development of diagnostic and prognostic prostate cancer biomarkers has the potential to dramatically improve disease management, reduce overtreatment, and eradicate death from this disease. PSA is currently the only serum marker in widespread clinical use, although its limitations are well established (54, 55). Perhaps surprisingly, the most clinically advanced prostate cancer biomarker is in fact an IncRNA. Prostate cancer antigen 3 (PCA3) is a unique, polyadenylated, atypical alternatively spliced IncRNA specifically overexpressed in >95% of primary prostate tumors (56). Urinary detection of PCA3 has been developed as a prostate cancer detection test with superior tumor specificity to PSA (57). The Progenesis PCA3 test is approved by the U.S. Food and Drug Administration and commercially available to aid in the decision of repeat biopsies. Correlations between PCA3 and prognostic factors (histologic Gleason grade and tumor stage) are conflicting, although most studies report the PCA3 test is negative in men with indolent cancer (58, 59). Efforts to improve the prognostic value of PCA3 are focusing on teaming it with TMPRSS2-ERG, a highly prostate cancer–specific family of gene fusion transcripts (60). Two independent prospective, multicenter evaluations of the combined quantification of PCA3 and TMPRSS2-ERG revealed that the superior prostate cancer specificity of this urinary biomarker panel over serum PSA could reduce a substantial number of unnecessary prostate biopsies (61) and could also have utility for risk stratification in an active surveillance setting (62).

Circulating small ncRNAs have bone fide appeal as blood/urine-based biomarkers, demonstrating resistance to variations in temperature and pH as well as endogenous RNase activity (63). Serum samples from men with low-risk, localized prostate cancer and metastatic CRPC have been shown to exhibit distinct circulating miRNA signatures (Fig. 2; refs. 64–66). Similarly, plasma miRNA panels have been shown to differentiate patients by tumor aggressiveness (67, 68). A common feature to these studies is the detection of miR-21, miR-141, and miR-375 in the plasma/sera of men with advanced disease and the association of these miRNAs with poor prognosis.

ncRNAs as prostate cancer therapeutics

Our ever-expanding appreciation of molecular tumor heterogeneity, coupled with transcriptomic profiling and mechanistic studies (that reveal widespread dysregulation of ncRNAs in prostate cancer), suggest bespoke treatments, which could be tailored to distinct molecular genotypes. miRNAs constitute one of the most abundant classes of gene-regulatory molecules (6). On one hand, these make these micromolecules highly attractive for therapeutic manipulation. Conversely, because many miRNAs are targeted by a single miRNA, off-target effects are likely to be substantial. A number of other major obstacles are impeding development of (nc)RNA-based therapeutics, such as the inherent low stability of RNA molecules and tumor-specific delivery and retention. Some solutions exist: Locked nucleic acid design, conjugation to cholesterol moieties, and encasement in nanoparticles have all been shown to improve stability. Targeted delivery to specific tissues can be achieved by linking tumor-specific ligands to nanoparticle surfaces. Prostate tumor cells could be selectively targeted through the cell-surface receptor PSMA (69). Nanoparticles can be further specified to target tissues by engineering their size so that they can only pass through the larger pores present in tumor–blood vessels, allowing them to accumulate inside tumor cells (70).

miRNAs seem particularly appealing from a therapeutic standpoint and can be manipulated in two ways: miRNA replacement and miRNA reduction (using antisense...
The aim of miRNA replacement is to reintroduce tumor-suppressor miRNAs depleted in the tumor (by use of a miRNA mimic), thus reactivating specific pathways to drive a therapeutic response. Given that evidence supports downregulation as the more widespread mode of miRNA dysregulation in prostate carcinogenesis (as opposed to oncoMir activation), this is an active area of research for novel prostate cancer therapeutics. Systemic delivery of atelocollagen-conjugated miR-16 in a mouse xenograft model of prostate cancer inhibited bone metastases. In an independent study, reintroduction of miR-15-16 induced tumor regression and enhanced docetaxel sensitivity in LNCaP cell lines and primary tumor cells. TP53 mutations are frequent in prostate cancer, and thus miR-34 (downstream effector of P53) replacement therapy could be of great therapeutic benefit. Systemic delivery of miR-34a was found to inhibit prostate cancer metastasis and improve survival in tumor-bearing mice.

Another approach utilizes a small RNA molecule as both a targeting (cell-type specific) and silencing moiety (via RNA interference) by generating an aptamer-siRNA chimera. The miRNA-processing enzyme Dicer acts upon the chimeric RNA, thus directing it into the RNA interference pathway, where it silences its target mRNAs. Aptamer-siRNA chimeras were designed to target prostate cancer cells specifically through interaction with PSMA at the cell surface, and effectively silenced two antiapoptotic genes (PLK1 and
BCL2) inducing tumor-regression in a mouse xenograft model of prostate cancer (69).

Far less is known on the potential of lncRNAs as therapeutic modalities for prostate cancer. It has been argued that truly effective treatment regimens must specifically target the subpopulation of prostate cancer stem cells. This avenue has recently been explored by targeting the telomerase lncRNA TERC, which was shown to be enriched in α2β1high CD44lhigh prostate cancer stem cells. A two-pronged "telomerase-interference" approach consisting of ectopic expression of a TERC (with a mutated template region) and an siRNA (against wild-type endogenous TERC) effectively reprogrammed telomerase, eliciting a DNA damage response and apoptosis (73). This novel approach was also shown to abrogate the tumorigenicity of DU145 α2β1high CD44lhigh prostate cancer cells in SCID mice (74).

Conclusions

The field of ncRNA biology and its contribution to human disease is experiencing a well-deserved upsurge in research activity. Differential expression of ncRNAs is now a recognized trait of prostate tumorigenesis; however, the functional role of many of these molecules unearthed during profiling studies remains underdetermined. We are only just beginning to understand how these noncoding molecules are involved in prostate cancer. Teasing apart their diverse range of target molecules and modes of action offers an unparalleled opportunity to open the drapes and shed light onto the altered biology of the so-called "dark matter" inside the prostate tumor cell. It was recently shown that prostate cancer cells are enriched in chimeric miRNAs, compared with their benign counterparts (75). One could logically extrapolate from these findings that chimeric ncRNAs might also be a prominent feature in prostate cancer. The decreasing cost of whole transcriptome RNA-Seq and its reciprocal increased accessibility to more laboratories will be instrumental in validating studies to date and addressing other questions too: What of the expression or role of piRNAs or even mitochondrial ncRNAs in prostate cancer? Is the elevated expression of snoRNAs in advanced prostate cancer simply a net result of elevated protein synthesis or are they playing a more sinister role? Relatively speaking, biomarker studies into prostate cancer ncRNAs are in their infancy. Further work is needed to establish the importance of distinguishing between free-circulating ncRNAs, those bound to Argonaute proteins and circulating microvesicle-encapsulated ncRNAs. The therapeutic applications of ncRNAs in prostate cancer are still in a formative stage and require extensive investigation in vitro and in animal models before their true potential can be realized.

Authors' Contributions

Conception and design: E.M. Bolton, A.S. Perry
Development of methodology: E.M. Bolton
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): E.M. Bolton, T. Lynch
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): A.S. Perry
Writing, review, and/or revision of the manuscript: E.M. Bolton, A.L. Walsh, T. Lynch, A.S. Perry
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): E.M. Bolton, T. Lynch, A.S. Perry
Study supervision: T. Lynch
Other (prepared figures): A. Tuzova

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