RNAi-based Cancer Therapeutics: Are we there yet?

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Abstract

RNAi-based therapeutics remains one of the most promising strategies for the effective cancer treatment due to its high target-specificity, precise mechanism of action, greater potency and reduced side effects. Although, tremendous progress and advances have been made in the past few years to develop nanotechnology-based efficient non-viral delivery systems, there are still many hurdles and challenges that must be conquered to achieve the target of clinically relevant formulation in terms of safety, specificity and efficacy.

Introduction

Cancer is the leading cause of death worldwide and according to WHO accounted for almost 8.2 million deaths in 2012 [1]. Clinically, chemotherapy plays a vital role in combating cancer, followed by surgery and radiotherapy. Chemotherapy involves the utilization of chemotherapeutic or cytotoxic agents, which are primarily employed to inhibit or control the rate of growth of tumor tissues. Despite, the availability of potent anti-cancer drugs in the clinic, by large, the use of these cytotoxic agents impose some limitations, such as the non-specific distribution at the tumor site, which results in the insufficient penetration of such drugs into the tumor tissues [2]. Next, the non-selective action of these agents results in the damage to the normal healthy cells, causing extreme side effects to the body and further limits the dose or its frequency of dosing [3]. Another important limitation associated with the use of cytotoxic agents is the development of multi-drug resistance (MDR) [4]. All these cases, overall reduces the efficacy of chemotherapeutic compounds.

RNAi in Cancer Therapeutics

RNA interference (RNAi), mediated by short double-stranded RNA (dsRNA) molecules is a sequence-specific post-transcriptional gene silencing phenomenon, resulting in the degradation of target mRNA and subsequently its expression [5]. In the last decade or so, the RNA interference (RNAi) technology, mediated primarily by small interfering RNA (siRNAs) and micro RNA (miRNAs) has emerged as one of the most promising strategies for cancer therapeutics [6-8], primarily due to its high specificity, precise mechanism of action and potency [9]. The strategy is also advantageous in terms of its capability to target multiple oncogenes simultaneously. In addition to this, the RNAi technology aids to improve the efficacy of chemotherapeutic agents by overcoming the multi-drug resistant (MDR) effects.

Challenges

Despite, some major advances in this field of therapeutics, there are, however some challenges that needs to be overcome, such as the biological safety, serum stability, off-target effects and effective in vivo delivery [10]. A significant progress has been made in terms of minimizing the off-target effects, thus improving the precision and safety of such drugs [11]. Various chemical-modifications to the oligonucleotide backbone have also been investigated, resulting in the improved serum stability [12]. From the in vivo delivery standpoint, even though the viral-based vectors showed promise [13,14], its safety has always been of concern and thus limits the use. In this scenario, the nanotechnology-based non-viral delivery vehicles became the preferred drug delivery choice [15], for its overall biological compatibility and enhanced in vivo delivery.

Nanotechnology-based Delivery Strategies

The nanotechnology-based strategies have made significant progress in the development of efficient non-viral delivery systems. Various promising nanoparticles (NPs) strategies that have been successful in depicting in vitro gene silencing and tumor reduction efficacy in animal models, safety in non-human primates and in few cases, have undergone clinical trial testing include. (A) Lipid based NPs: liposomes [16], lipoplexes [17,18], stable nucleic acid lipid nanoparticles (SNALP) [19,20] & lipidoid [21], polycation liposomes [22,23], (B) Polymeric NPs: both natural and synthetic, includes cyclohextrin [24], chitosan [25], PLGA [26], polymeric micelles [27], PEI [28] & dendrimers [29], (C) Inorganic NPs: calcium phosphate CaP [30], (D) Carbon-based materials, carbon nanotubes (SWNTs, MWNTs) [31,32], (E) Metal nanoparticles – Gold (Au) [33], Quantum dots (QDs) [34], silicon-based nanoparticles (MSNPs) [35] & super paramagnetic iron oxide nanoparticles (SPIONs) [36] etc. In addition to this, atelocollagen-based delivery strategy also proved to be successful in few cases [37,38].

To develop a clinically-relevant effective nanoparticles delivery system, the nanoparticles (NPs) formulation also needs to overcome various extracellular and intracellular hurdles [39] such as, stability in blood serum, greater half-life for high enhanced permeability and retention (EPR) effect, ability to escape the reticuloendothelial system (RES), selective accumulation and penetration into the tumor tissues and final binding to the target tumor cells. The NPs must then be taken up the cells by the process of endocytosis, followed by the release of the intact siRNA in the cytoplasm by endo-lysosomal escape. The final step is the sequence-specific binding to the target mRNA and gene knockdown.
Current State of Clinical Trials

In recent times, RNAi based therapeutics has rapidly progressed from benchside to the patients in clinic. Currently, there are many clinical trials in progress, most of them in Phase-I/IIa, evaluating the safety and efficacy of such siRNA-based drugs for cancer therapeutics [40-44]. The detailed description of the various ongoing clinical trial programs is mentioned in Table 1.

Table 1: Current RNAi based cancer therapeutics in clinical trials.

<table>
<thead>
<tr>
<th>Company</th>
<th>Prog.</th>
<th>Target Gene</th>
<th>Delivery System</th>
<th>Disease</th>
<th>Stage of Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alnyum Pharmaceutical als</td>
<td>ALN- VSP02</td>
<td>VEGF, KSP</td>
<td>Lipid Nanoparticle s (LNPs)</td>
<td>Liver Cancer</td>
<td>Phase-I Complete</td>
</tr>
<tr>
<td>Calando Pharmaceutical als</td>
<td>CALAA-01</td>
<td>RRM2</td>
<td>Cyclohexatin polymeric Nanoparticle s</td>
<td>Solid tumors</td>
<td>Phase-I Terminated</td>
</tr>
<tr>
<td>Enzon Pharmaceutical als</td>
<td>EZN-29</td>
<td>HIF-1α</td>
<td>Naked LNA antisense</td>
<td>Solid Tumors</td>
<td>Phase-I Complete</td>
</tr>
<tr>
<td>Gradalis</td>
<td>FANGT M Vaccine</td>
<td>furin</td>
<td>Plasmid encoding bi-shRNA</td>
<td>Advanced Cancer, Melanoma</td>
<td>Phase-I Complete/II</td>
</tr>
<tr>
<td>Silence Therapeutics</td>
<td>Alu027</td>
<td>PKN3</td>
<td>Liposome-siRNA complex</td>
<td>Pancreatic, Advanced solid tumors</td>
<td>Phase-I/IIa</td>
</tr>
<tr>
<td>Sildenafil</td>
<td>siG12D</td>
<td>LODER</td>
<td>Biodegradable polymer matrix</td>
<td>Adenocarcinoma of pancreas</td>
<td>Phase-I/IIa</td>
</tr>
<tr>
<td>Santaris Pharma</td>
<td>SPC299</td>
<td>Bcl-2</td>
<td>Locked nucleic acid (LNA)</td>
<td>Chronic Lymphocytic Leukemia</td>
<td>Phase-I/II</td>
</tr>
<tr>
<td>Tekmira</td>
<td>TKM-PLK1</td>
<td>PLK1</td>
<td>Lipid Nanoparticle s (LNPs)</td>
<td>GI-NET, ACC, HCC</td>
<td>Phase-I/IIa</td>
</tr>
</tbody>
</table>

showed great potential and warrant its clinical development; however, to date, the success for such existing systems has been limited, primarily due to the toxicity issues and some additional challenges associated with the various stages of the delivery process. Hence, to further our understanding and progress in the field & to develop the clinically relevant RNAi formulation, it would thus be beneficial to develop a novel, safe, biocompatible, efficacious and multifunctional nanoparticle systems as personalized medicine for the near future.

References
