Chemical Sciences Journal
ISSN: 2150-3494

Innus, Chem Sci J 2017, 8:2
DOI: 10.4172/2150-3494.1000e117

Editorial OMICS International

Antisense Cancer Therapy: Do Antisense Oligonucleotides Hold Promise as a Cure for Cancer?

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Cancer is a dreadful disease causing a major percentage of deaths all over the world. Cancer is the second leading cause of death in the United States, trailing cardiovascular disease. According to National Cancer Institute statistics, over half a million deaths and a million and half new cases are predicted in the year 2017 [1]. The human body is composed of trillions of cells, and they perform specific functions with the aid of proteins. Genes impact the production of these proteins, and an error contained in these genes can yield aberrant versions of these proteins. In some cases, this can result in cancer. A newly diagnosed patient is often concerned for the following reasons: 1) they are afraid of cancer treatments being costly, 2) cancer survival rates are sometimes low and chances of reoccurrence of some cancers are high, and 3) the false paradigm that cancer is incurable.

Until modern times, cancer diagnosis and treatment exhibited very low success rates. Over the centuries, our understanding of cancer improved and new strategies for combatting cancer were created. Certain types of cancers are fully treatable and others could be prevented if diagnosed at the early stage. Despite tremendous efforts by researchers, fighting cancer is very challenging because there is an enormous similarity between diseased cells and healthy cells. Detection is the first step to defeat cancer. Fortunately, modern advancements in medicine provide ways to perform early stage diagnosis of cancer. For example, imaging tests, mammography, cytology, biopsy, and Pap smears [2]. The importance of early diagnosis of cancer relies in the virtue of cancer. Unlike other diseases, cancer invades its surrounding environment and spreads to other parts of the body. This is known as metastasis, which compounds the difficulty in treatment. Several techniques (invasive & non-invasive) are used to image cancer, but commonly used techniques are MRI and PET scan, but these techniques are expensive and not ideal for routine checkups. Relentless efforts in biomedical research have improved the effectiveness of non-invasive imaging techniques and made them cost effective. Several groups have been working on fluorescence imaging techniques in biomedical sciences to design effective and cheap strategies to image cancer. Innus Mohammad and co-workers developed a strategy to image hypoxic regions in tumor cells utilizing Indocyanine Green bis-acid [3]. Several other groups are working in this area to improve the effectiveness of non-invasive detection of cancer at early stage [4-7]. After the detection, doctors suggest the appropriate treatment procedures to patients. The most common treatments for cancer are a) surgery, b) chemotherapy, c) radiation therapy, and d) targeted therapy.

Surgery is frequently used to diagnose and treat breast cancer, but surgical treatments have side effects such as pain, infection, loss of organ function, bleeding, and blood clots. Some tumors are difficult to access during the surgery and can't be removed completely. The remaining tumorous tissue has a greater risk of tumor regrowth. As an alternative to surgery, chemotherapy drugs are developed based on the idea of targeting cell division of rapidly growing cells. Unfortunately, there are other cells that grow rapidly in our body including: hair, gastrointestinal epithelia and bone marrow. As a result, patients undergoing chemotherapy experience hair loss and gastrointestinal problems. In radiation therapy, tumors are exposed to high energy radiation to kill cancer cells. Although the current advanced techniques minimize the effect of radiation on healthy cells, it has several side effects depending on the location of the tumor, such as skin problems, breathing problems, and sometimes the risk of developing a secondary cancer. The combination of these above mentioned therapies increase cancer survival rates, but side effects are still perilous.

New therapeutic strategies/models are necessary to reduce or eliminate toxic side effects. New advancements in cell biology, availability of human genome sequences and recent developments in oligonucleotide synthesis has opened the door for a targeted therapy called "antisense therapy". The first experimental evidence for antisense therapy was provided by Paul C. Zamecnik in 1978 [8]. In antisense therapy a single stranded oligonucleotide (DNA or RNA), which is a complimentary sequence of gene responsible for disease, is introduced into the cells to selectively turn the gene off. Antisense oligonucleotides are chemically modified or unmodified single stranded DNA/RNA molecules. Upon introduction, it is expected that complimentary oligos hybridize with the sequence of target mRNA and prevent further translation and protein synthesis. Three different approaches are adapted by the researchers to block the translation of mRNA, 1) antisense oligonucleotides, 2) ribozymes, and 3) short interfering RNA (siRNA). Ribozymes are RNA molecules with catalytic activity. When these molecules bind target mRNA, the phosphodiester backbone gets cleaved and the mRNA becomes deactivated. Short interfering RNA (siRNA) is a double stranded synthetic RNA that is designed to silence the particular gene by mRNA degradation. The goal of all these molecules is to hijack protein synthesis at the level of translation to cure genetic disorders.

Although the idea behind antisense oligonucleotide therapy sounds extraordinarily simple, there are several challenges associated with this approach (Figure 1). Despite two decades of extensive research, only two RNA therapeutic drugs were approved by FDA, Fomivirsen and Kynamro. The main hurdle that slowed the progress of antisense drugs is lack of methods to design endonuclease stable oligonucleotides and delivering them efficiently into the cells. Due to lack of efficacy and immune reactions to the treatments, early attempts to introduce naked oligonucleotides experienced a setback. As a result of recent improvements in oligonucleotide deliveries for antisense therapy (for example, N-Acetylgalactosamine conjugate and nanoparticle-based approaches), more and more companies are actively taking part in

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Received May 25, 2017; **Accepted** May 27, 2017; **Published** June 12, 2017

Citation: Innus M (2017) Antisense Cancer Therapy: Do Antisense Oligonucleotides Hold Promise as a Cure for Cancer?. Chem Sci J 8: e117. doi: 10.4172/2150-3494.1000e117

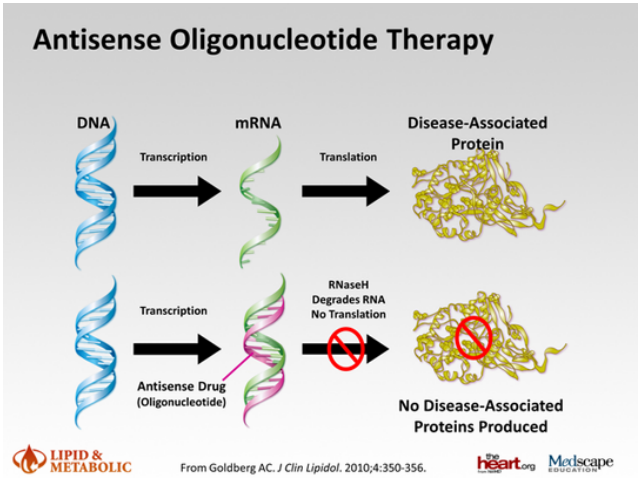

Figure 1: Cartoon representation of the antisense oligonucleotide therapy mechanism.

antisense therapeutic research [9-22]. Currently, over a hundred oligonucleotides are in clinical trials from 30 different pharmaceutical companies [23]. The resurgence of antisense therapy looks promising, with key players in the field are anticipating drugs to hit the market very soon.

Along with working towards better strategies to defeat cancer, I believe that informational sessions for cancer patients to create hope is also very important. As mentioned earlier, creating awareness about the modern advancements in the medical field and the availability of new classes of treatments helps to allay patients' fear. There is a war quote by Sun Tzu: *"Victorious warriors win first and then go to war, while defeated warriors go to war first and then seek to win."* Helping a patient understand their options and how treatment is often successful can improve patient outlook and tolerance of treatments.

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