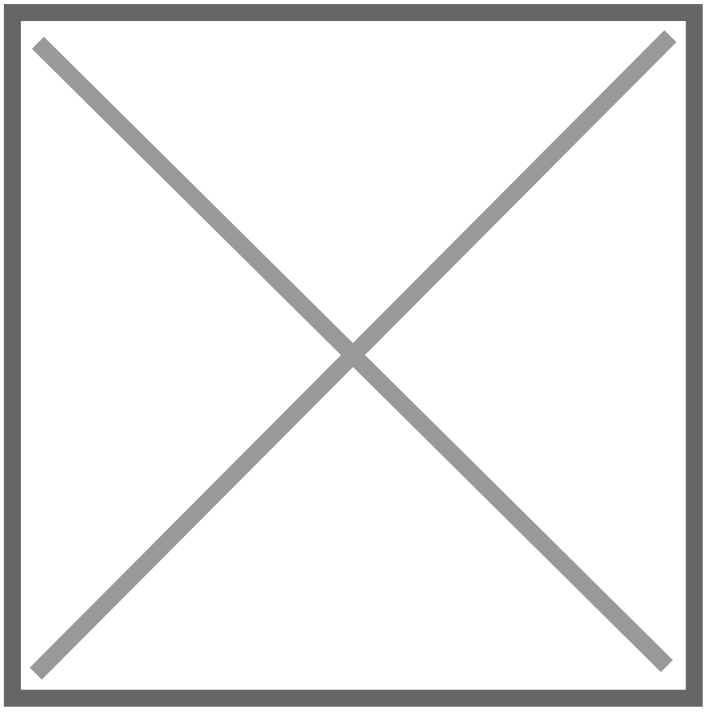
BioSpect
the business of Bi
24 years of leveraging the business of Bio
www.biospectrumindia.co

RNAi Therapy, Enhancing Therapeutic Treatments

10 March 2009 | News



RNAi Therapy, Enhancing Therapeutic Treatments

Discovered in 1998 by Craig Mello and Andrew Fire, RNA interference is heralded as a major scientific breakthrough in the past decade and was awarded the Nobel Prize for Physiology or Medicine in 2006.

Also known as gene silencing RNA interference involves the use of double stranded RNA (dsRNA). Once inside the cell, this material is processed into short 21-26 nucleotide RNAs termed siRNAs that are used in a sequence-specific manner to recognize and destroy complementary RNA, effectively switching off the activity of the gene and halting production of the protein for which it codes. This activity is being developed as a potential antiviral therapeutic strategy. However, therapeutic strategies using RNAi against viruses that cause chronic infections, such as human immuno deficiency virus (HIV) and hepatitis B or hepatitis C, are more difficult to design, but studies have begun to address identifiable problems.

Developments and history

RNAi technologies include chemical synthesis by in vitro transcription and use of plasmid or viral vectors. DNA-directed RNAi (ddRNAi) is used to produce dsRNA inside the cell, which is cleaved into siRNA by the action of Dicer, a specific type of RNAse III. MicroRNAs are derived by processing short hairpins that can inhibit the mRNAs. Expressed interfering RNA (eiRNA) is used to express dsRNA intracellularly from DNA plasmids.

Since its discovery, many companies have started to develop therapies based on the Nobel Prize winning RNAi technology and Alnylam Pharmaceuticals is spearheading the business of RNAi-based therapeutics. The company has to its credit the maximum number of collaborations and has received maximum funding in the RNAi segment. It currently has one product, ALN-RSV01, in clinical development, which is in phase-II trials for respiratory syncytial virus (RSV). In addition, the company is developing RNAi therapeutics for the treatment of influenza, hypercholesterolemia, and liver cancers, among other diseases. The company teamed up with Isis Pharmaceuticals to form Regulus Therapeutics, a company focused on developing new drugs based on microRNA. MicroRNA is one of two types of RNA interference found in all human cells and affects how genes are turned off and on. MiRNAs regulate whole network of genes; therefore therapeutics based on this technology represent a new approach to target the pathways of disease. SR Pharma subsidiary Atugen developed RTP-801i and later licensed it to Quark Biotech. The drug prevents the functioning of the gene REDD-1 that is linked to the progression of wet age-related macular degeneration (AMD) where aberrant blood vessels beneath the retina leak blood and fluid into the eye causing loss of vision.

In April 2008, GlaxoSmithKline and Regulus Therapeutics announced a $600 million alliance to discover, develop and market microRNA-targeted therapeutics to treat inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease. Calando Pharmaceuticals, a majority-owned subsidiary of Arrowhead Research Corporation based in California, US, has its lead candidate,

CALAA-01, in phase-I clinical trials, the results of which are expected in 2010. The drug is a nanoparticle that contains small interfering RNA (siRNA) that targets the M2 subunit of ribonucleotide reductase, a well-established cancer target. Its nearest competitor in the field of cancer therapies based on RNAi is Silence Therapeutics.

A subsidiary of Silence, called Atugen, along with partners Quark Biotech and Pfizer is currently investigating a siRNA therapy for wet AMD. RTP-801i is currently in phase-I clinical trials. There are no marketed siRNA drugs, RTP-801i is indeed the fourth to enter clinical trials. Sirna Therapeutics was the first company to take a siRNA drug into trials. It had two drug candidates in clinical development, which include one that also treated AMD, when Merck & Co recently bought it in a deal worth $1.1 billion. Merck & Co has also, in the past, signed collaboration deals with SR Pharma and Alnylam Pharma. Sirna Therapeutics was the first company to take a siRNA drug into trials. It had two drug candidates in clinical development, one for AMD and one for hepatitis C, when Merck & Co bought it this year, in a deal worth $1.1 billion. Opko was formed when Acuity Pharmaceuticals an Froptix Corporation merged in March 2007 has the most advanced siRNA therapy, this time to treat AMD and diabetic macular edema (DME), bevasiranib has completed phase-II trials.
Biotech company Nucleonics has recently been cleared by the FDA to begin a phase-I trial of its RNAi based therapy for hepatitis B. Slightly different to the others, this therapy uses strands of DNA which, once in the body, produce siRNA and is dubbed expressed interfering RNA (eiRNA). An Australian company called Benitec has a drug designed to target HIV/AIDS, is in phase-I clinical development.

Future

RNA interference continues to offer significant promise for a host of therapeutic treatments. Potentially any disease-causing gene, cell type or tissue can be targeted with RNAi, including those not ‘druggable’ with small molecules or protein-based therapies. Pharma companies are increasingly investing in siRNA optimization or examining siRNA alternatives, in addition to staking out proprietary positions in lipid-based, nanotransporter-based and alternative delivery technologies. The development and licensing of such platforms will become crucial for developers over the coming years. Although several researchers have tried to develop the therapeutic potential of RNA interference technology, the limited success of various delivery methods such as viral mediated delivery and intravenous injection hampered its wider application.
Being based on natural molecules, RNAi drugs hold a number of advantages over traditional drugs, both small molecules and biopharmaceuticals. RNAi drugs can eliminate years of screening and the drug candidates can get into the clinic very quickly. Not only does this save money, but it could also extend the patent life of the drug while it’s actually in the market. The drugs also don’t need to be stabilized like many other therapies based on RNA molecules. Further research and subsequent clinical trials directed at finding safe and effective in vivo delivery methods for therapeutic siRNAs will be crucial.

Jahanara Parveen