RNAi-Based Therapeutics: A Novel Platform for Drug Development

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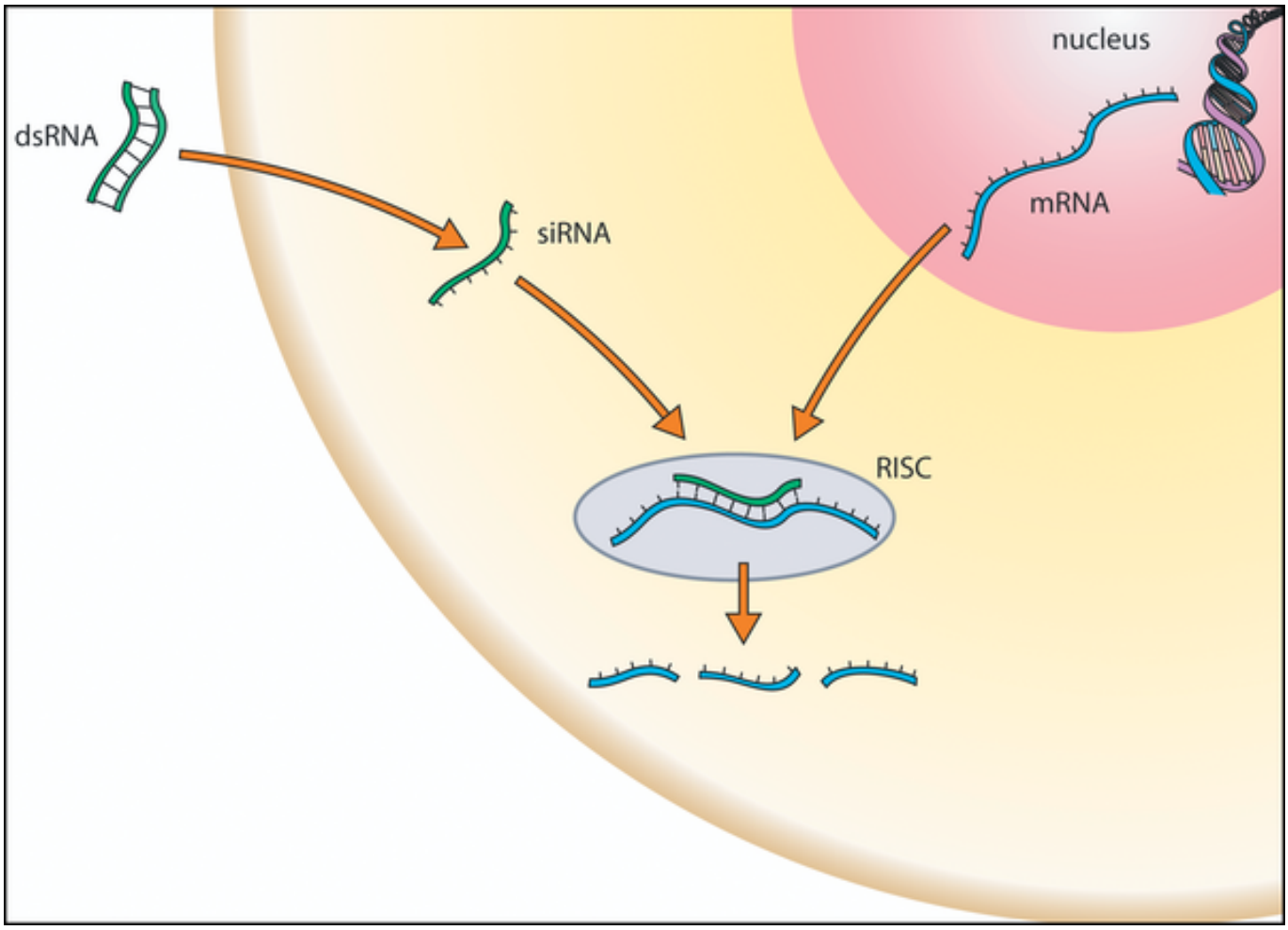

A wide range of medical conditions result from the overexpression of specific proteins. For example, it is known that both hypertrophic scarring and retinal scarring are consequences of the excessive expression of connective tissue growth factor (CTGF), an extracellular matrix protein that plays a key role in tissue generation and repair. The ability to mitigate the expression of proteins, such as CTGF, is therefore desirable for the development of a new class of therapeutics for scarring as well as for many other indications for which there is a current unmet need.

The RNAi mechanism

The discovery of a naturally occurring process known as RNAi (short for “RNA interference”)—for which Dr. Craig C. Mello and Dr. Andrew Z. Fire shared the 2006 Nobel Prize in Physiology or Medicine—has enabled a new platform for drug development that can potentially serve as a basis for the creation of new types of therapeutics. With RNAi, short double-stranded RNAs interfere with the expression

of targeted genes. The development of therapeutics based on this technology potentially allows for the reduction of expression of any one of thousands of human genes in living cells and the proteins that are produced as a result.

To better understand the potential of the RNAi mechanism as a basis for drug development in greater depth, recall that in order for a gene to guide the production of a protein, it must first be copied into a single-stranded chemical messenger (mRNA), which is then translated into the corresponding protein. The abnormal expression of certain genes—too much expression or too little—can result in disease, as can the expression of an abnormal protein from a gene with a mutation. In a highly specific way, RNAi causes a particular mRNA to be destroyed before it is translated into a protein.

The process of RNAi can be artificially induced by introducing a small double-stranded fragment of RNA that corresponds to a particular mRNA into a cell. A protein complex called RISC (RNA-Induced Silencing Complex) recognizes this double-stranded RNA fragment and uses one strand, the guide strand, to bind to and destroy its corresponding cellular mRNA target. If the mRNA is destroyed this way, the encoded protein cannot be made. Thus RNAi provides a way to potentially block the expression of specific proteins.

A tool to treat human disease

Since the overexpression of proteins plays a role in many diseases, the ability to inhibit gene expression with RNAi provides a potentially powerful tool to treat human disease, offering high specificity for selected gene targets; high potency/low doses; the ability to interfere with the expression of potentially any gene; the accelerated generation of lead compounds; and low toxicity.

A successful RNAi therapeutic platform will include stable, specific and potent RNAi compounds and the ability to deliver these compounds to the tissue(s) of choice. One conventional solution to the delivery problem involves encapsulation into a lipid-based particle, such as a lipid nanoparticle, to improve circulation time and cellular uptake. However, researchers have also utilized an alternative approach to delivery in which drug-like properties are built into the RNAi compound itself without the use of these lipidic carriers/vehicles. These novel compounds are termed “self-delivering” RNAi compounds or sd-rxRNA.

Innovation in drug delivery

The combination of chemical modifications that results in spontaneous cellular uptake of sd-rxRNA without the need for a delivery vehicle was discovered through systematic medicinal chemistry screening. sd-rxRNAs are hybrid oligonucleotide compounds that combine the beneficial properties of both conventional antisense technologies and the newer RNAi approach. Traditional, single-stranded antisense compounds have favorable tissue distribution and cellular uptake properties. However, they do not have the intracellular potency that is a hallmark of double-stranded RNAi compounds. Conversely, the duplex structure and hydrophilic character of traditional RNAi compounds results in poor tissue distribution and

cellular uptake.

In an attempt to combine the best properties of both technologies, sd-rxRNA has a single-stranded phosphorothioate region and a short duplex region, and contains a variety of nuclease-stabilizing and lipophilic chemical modifications. The combination of these features allows sd-rxRNA to achieve efficient spontaneous cellular uptake and potent, long-lasting intracellular activity.

The treatment of multiple cell types with fluorescently labeled sd-rxRNA demonstrates the efficient and universal cellular uptake achieved with this technology. All cell types tested—primary, neuronal and non-adherent—internalize sd-rxRNA compounds uniformly and efficiently. Potent and long-lasting silencing of targeted genes has been demonstrated in many cell systems. Efficient cellular uptake is observed both *in vitro* and *in vivo*, including into tissues such as skin and retina following local administration, and liver following systemic delivery. Data suggest that efficient uptake of sd-rxRNA compounds might be achieved in any tissue, as long as the route of administration enables local delivery of the compound. This may enable rapid progression toward a pipeline of clinical programs in a wide range of diseases, where local administration is an option. The built-in drug-like properties of sd-rxRNAs may make them amenable for systemic delivery.

RNA therapeutics in the pipeline

According to a 2015 review of RNA-based therapeutics in *Genetic Engineering & Biotechnology News*, there are many RNA therapeutics currently in the drug development pipeline. For example, RXI-109, the lead sd-rxRNA compound developed by RXI Pharmaceuticals, was designed to specifically silence the CTGF protein to reduce dermal and ocular scarring. The company has also harnessed the capabilities of sd-rxRNA to develop cosmetic product candidates, including RXI-185, which targets Collagenase, an enzyme that breaks down the peptide bonds in collagen, and RXI-231, which targets Tyrosinase, a key enzyme involved in the synthesis of melanin.

Gradually it is becoming clear from clinical testing that RNAi-based technology may allow the development of therapeutics with significant potential advantages over traditional drugs as well as offer totally new and selective treatment approaches for diseases that lack adequate therapies today. It is not anymore a matter of “if” but “when” we will see the first RNAi based drugs come to the rescue of patients with difficult to treat diseases.

About the author

Geert Cauwenbergh, Dr. Med. Sc. is President and CEO of RXi Pharmaceuticals Corporation, a clinical-stage RNAi company developing innovative therapeutics in dermatology and ophthalmology that address significant unmet medical needs.

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