

Frequently asked questions

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TRANSFORMATIONAL
MEDICINE

Describe Cequent Technologies

An early-stage biopharmaceutical company, Cequent is pioneering the development of novel therapeutics to prevent and treat a wide range of human diseases – from inflammatory diseases to cancer – based on the company’s proprietary technology, TransKingdom RNA interference (tkRNAi™). Cequent’s first products, now in pre-clinical development, are drug candidates targeting colon-cancer prevention and inflammatory bowel disease. The company designed its powerful tkRNAi technology to deactivate specific disease-causing genes safely and effectively, using non-pathogenic bacteria as an engine to produce and deliver RNAi directly into cells. It is based on ground-breaking scientific research originating at the Beth Israel Deaconess Medical Center/Harvard Medical School. A privately held company based in Cambridge, Massachusetts, Cequent was established in 2006.

What is the promise of RNAi and why is it a hot topic in medicine right now?

Hailed as “a revolution in biology,” RNAi is arguably the most promising medical breakthrough of the decade – the subject of the 2006 Nobel Prize in Physiology or Medicine. Its discovery has created the opportunity to address targets that were previously difficult to treat, and develop an entirely new class of therapeutics that work by effectively deactivating the specific gene or genes implicated in the progression of a disease. Since RNAi is highly specific, many believe it will be a catalyst for achieving “personalized medicine,” where, for example, a cancer drug would be tailor-made based on the molecular character of a particular patient’s tumor. Despite the promise, however, one major difficulty that has to date impeded the wider development of RNAi-based therapies is the need to deliver the molecules triggering RNAi into the target cells and diseased tissues.

What is Cequent’s tkRNAi technology, and how does it actually work?

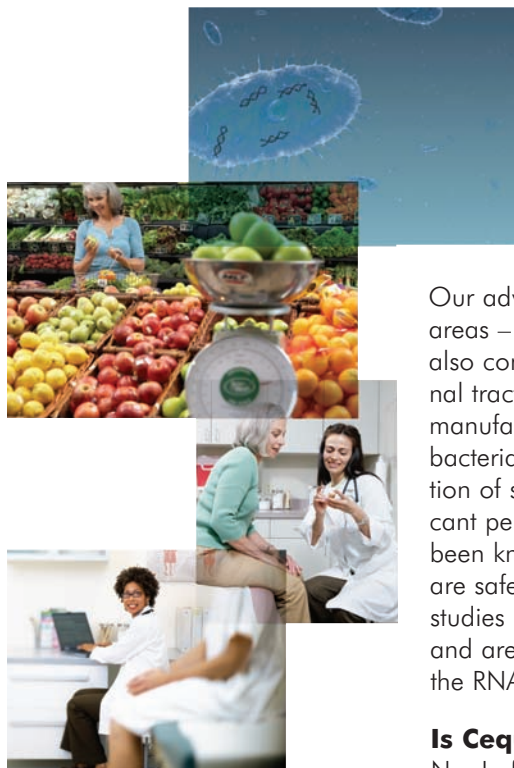
Our tkRNAi technology offers an elegant solution to the problem of delivering RNAi therapeutics. In a proprietary process, we modify live, nonpathogenic bacteria to produce and deposit mediators of RNAi directly into the target cells. The nonpathogenic bacteria are subsequently degraded by the host cells without adverse effects, and eliminated by the body through its own natural processes. This method has been shown to induce targeted gene silencing (in other words, it disables the “bad” gene or genes that cause disease, without affecting the surrounding genes), delivering significant therapeutic effects in multiple model systems, including live animals. All of the clinical drug candidates in our pipeline are based on this tkRNAi technology.

Does giving E. coli to humans pose a risk?

No. In fact, we use a strain of E.coli used as a health supplement in some countries. Escherichia coli (E. coli) is one of the main species of bacteria living in our intestines, where it helps our bodies break down and digest the food we eat. There are hundreds of strains of E. coli, and most are harmless. (One particular strain, E. coli O157:H7, is responsible for the recent cases of serious foodborne illness.) The US Food and Drug Administration has already approved the use of bacteria as delivery vehicles (vectors) for other uses in the body, notably vaccines. Our tkRNAi technology takes advantage of the beneficial properties of “healthy” E. coli bacteria; we genetically modify a safe, nonpathogenic strain to produce and deliver RNAi directly into cells.

How does Cequent’s approach differ from that of its competitors, and what advantages does it offer?

In order to achieve therapeutic effects, the mediator molecules of RNAi (short interfering RNA, or siRNA) need to be inserted into the target cells, but delivery of these siRNA has been a major challenge. Consequently, most RNAi-therapeutics companies have been focused on organs into which delivery is fairly straightforward – including the eye, liver, and lung (through inhaled siRNA) – excluding a host of devastating diseases that should be amenable to RNAi therapy. Our proprietary tkRNAi technology is uniquely suited to deliver RNA interference to a number of organ systems that have been notoriously difficult to reach with other RNAi-based therapies – including the gastrointestinal tract, genitourinary tract, and the skin. To date, none of the company’s competitors have offered a method for delivering RNAi into these key areas. We solve the delivery problem by using live nonpathogenic bacteria to produce and deliver mediator molecules of RNA interference directly into target cells.



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Our advanced pre-clinical programs currently target two important gastrointestinal disease areas – inflammatory bowel disease, and polyposis, a precancerous condition. We are also conducting ongoing research for a number of indications outside of the gastrointestinal tract. Advantages of our tkRNA technology include the considerably lower costs of manufacture: we use a cost-effective fermentation process to replicate the RNAi-producing bacteria, while other RNAi methods require large-scale synthesis and chemical modification of siRNA. In addition, we believe our bacterially based tkRNAi technology has significant performance and safety advantages over harder-to-predict viral vectors, which have been known to cause problems through uncontrolled replication. Our therapeutic bacteria are safe and easy to control: they are modified to prevent pathologic replication, and our studies have shown that once they have delivered their payload into the cell, they degrade and are eliminated by the body's own natural processes. Should the clinician want to stop the RNAi treatment, the bacteria can simply be eradicated with regular antibiotics.

Is Cequent's approach the same as gene therapy?

No. In fact, RNAi-based therapy takes a very different approach. The goal of gene therapy is to *replace* dysfunctional or missing genes required to perform a critical function in the body; the lack of the functioning gene causes disease. For example children with "Bubble Boy" disease (X-SCID Severe Combined Immunodeficiency) have a faulty copy of a gene on their X chromosome that makes an immune protein called interleukin-2, leaving them with no resistance to infection. Gene therapy would try to replace the missing gene.

By contrast, we designed our tkRNAi technology to *suppress* a specific function of a gene that is responsible for progression of a disease. An oncogene is an example of a promising target for RNAi therapy. (An oncogene is a gene that contributes, when active, to the production of a cancer, for example by enabling the cell to grow uncontrollably or to resist a therapeutic drug treatment.) By deactivating the oncogene's processes in the cell, RNAi can stem its negative effects – eliminating the cancer cell's proclivity to grow uncontrollably, or making it more vulnerable to treatment or to the body's own immune system. Another important difference between our technology and gene therapy is the use of different carrier systems (called vectors). In most gene-therapy studies, a "normal" gene is inserted into the genome to replace an "abnormal," disease-causing gene using a vector to deliver the therapeutic gene to the patient's target cells. Currently, the most common vector is a virus that has been genetically altered to carry human DNA. In some cases, viruses have caused severe side effects and even death in gene-therapy patients because they replicated uncontrollably. In our tkRNAi process, we use a nonpathogenic bacterial vector that is safe and easy to control. Should the clinician want to stop the RNAi treatment, the bacteria can simply be eradicated with regular antibiotics.

What is likely to be Cequent's first clinical application of the tkRNAi technology?

We currently have drug targets in advanced stages of pre-clinical development for colon-cancer prevention and inflammatory bowel disease. The first indication will likely be to treat people with familial polyposis (FAP), a devastating inherited gastrointestinal disease that causes hundreds of polyps to form in the colon. Today, without prophylactic removal of the colon, people with FAP almost inevitably get colon cancer, and their life expectancy is greatly reduced.

What is Cequent's corporate status?

A privately held company, Cequent closed a Series A financing in June 2007 with four venture capital firms: Ampersand Ventures, New England Partners/Nexus Medical Partners, Pappas Ventures, and Novartis Option Fund.

Who are Cequent's key management personnel?

Peter D. Parker – President & CEO
Chiang J. Li, MD – Founder & Director
Lisa A. Velardo – Chief Financial Officer
Susie Truong – Director, Finance & Administration

Johannes H. Fruehauf, MD, PhD – Director, Pre-clinical & Clinical Development
Jens Harborth, PhD – Associate Director, RNAi Research
Natalya Bodyak, PhD – Group leader, *In Vivo* Biology
Moreshwar Vaze, PhD – Group leader, Microbiology
A.J. Wang, PhD – Group leader, Molecular Biology