



DNAi[®]-Based Medicines

DNA interference (DNAi) looks set to break through the barriers that have previously hampered the development of DNA-related therapies.

By Dr Richard D. Gill at ProNAi Therapeutics, Inc



Dr Richard D. Gill is President and CEO of ProNAi Therapeutics, Inc. He has over 25 years of strategic management, research and commercialisation experience in the life sciences industry, and has an extensive track-record in starting and building businesses, as well as facilitating company turn-arounds in both the public and private sectors. Prior to joining ProNAi, Dr Gill was the President and CEO of Signet Laboratories, where he was instrumental in increasing company revenues and enhancing its value proposition, with a successful sale to Covance. In addition, he has headed up AnVil, Inc, ActiveCyte, Inc, and Genome Therapeutics (now Oscient Pharmaceuticals).

For many years, the promise of DNA-related therapies has gone largely unfulfilled, due to a daunting number of obstacles – lack of specificity and potency, high manufacturing costs, and the inability to deliver effective doses of DNA-based drugs. Other recent efforts in nucleic acid research and development, particularly in cancer, have focused on RNA rather than DNA. Current RNAi and antisense treatment approaches concentrate on binding to messenger RNA (mRNA) to slow or stop disease progression. However, because mRNA molecules are continually synthesised from a disease gene, the need for destruction of the molecule must be continuous for it to remain effective.

At ProNAi, for example, we have successfully overcome previous obstacles to the development of DNA therapies and are leveraging a novel, proprietary nucleic acid-based interfering technology, DNAi, to advance a next generation of therapies for the treatment of cancer and other complex genetic diseases.

DNA INTERFERENCE

DNA interference (DNAi) represents a novel approach to targeting known oncogenes, as well as specific genes involved in other diseases. It forms the basis of a new class of nucleic acid-based drugs whereby single strands of DNA are employed to target and treat non-transcribed regions of genomes responsible for genetic diseases.

The overall impact is similar to that of antisense and RNAi products but, because it works at the level of DNA, the product candidates have significant potential advantages. By acting at the DNA level, where only one or two copies of the gene exist per cell, treatment can be targeted more efficiently. With fewer targets, the activity of a DNAi drug can be expected to last longer at lower doses, and reduce some of the toxicity issues apparently prevalent with some other therapies. Additionally,

DNA-related therapies could also be more cost-effective to produce.

DNAi is radically different from competing approaches such as antisense, decoy, RNAi, shRNA, triplex, immunostimulators, and other nucleic acid drug approaches, and displays significant potential advantages over each. For example, current RNAi and antisense treatment approaches require continuous destruction of the mRNA for therapy to remain effective; this means RNAi drugs need high doses, which in turn means higher toxicity as well as cost – and this comes on top of the problems with delivery. DNAi eliminates this issue entirely, by focusing on the gene itself, channeling therapies one level up where ‘less is more’ in terms of drug dose and effectiveness.

A DRUG DESIGN ENGINE

ProNAi is also using its DNAi technology as a drug design engine (DNAi-HiT[™] Platform). The technology has displayed a number of benefits in the development of novel therapies. These include the following:

- ◆ The technology is being used to discover and validate therapies in a number of disease categories. While we will initially focus on advancing cancer therapies, other treatments for genetic diseases are also being considered.
- ◆ The resulting DNA-related product candidates exhibit specificity and selectivity, and can anneal directly to a diseased gene. This can potentially reduce side-effect and toxicity issues.
- ◆ By targeting DNA, the lead identification time for new product candidates can be shortened. Therefore, by using the genomic information secured through the Human Genome Project, we can more effectively design targeted therapies. This eliminates the need to



screen a large chemical library to identify a few compounds that 'hit' a particular protein, as is the case in the identification of small molecule therapies.

- ◆ We are also able to pursue disease targets that were previously thought untreatable. While targets for some diseases are apparently inaccessible to small molecules, they can be potentially targeted and destroyed at the level of DNA.

PRODUCT PIPELINE

Multiple DNAi-based drug candidates are currently in development with the potential to treat multiple cancers, including non-Hodgkin's lymphoma, prostate, melanoma, breast and colon cancers. Our lead drug candidate, PNT-100, has demonstrated *in vivo* efficacy in a variety of human tumour xenograft models; the product is scheduled to enter clinical trials in 2007 for the treatment of multiple cancers. We are also developing proprietary cancer therapies that would be compatible with current chemotherapeutics and could be used initially in combination therapy. In addition, the potential of DNAi-based therapies is being explored for indications such as inflammatory and neurodegenerative diseases.

DNAi DELIVERY

The successful delivery of nucleic acid-based drugs has been the 'holy grail' of the industry for many years. To overcome this problem, we have concluded an exclusive agreement with Novosom AG (Halle, Germany) for the licensing of their SMARTICLES® liposome delivery technology for use in all human diseases targeted by our PNT100 drug candidate. An option is also included for four additional DNAi targets. Through this partnership, we have developed a GMP-enabling oligo delivery method that will allow us to submit an IND, and we expect more significant milestones to be met in the near future.

CONCLUSION

In the past, various companies and researchers have investigated DNA therapies to treat diseases; however, due to the lack of specificity and potency as well as high manufacturing costs and drug delivery issues, these efforts are languishing, or have failed and been abandoned.

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