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QPS White Paper

RNAi Therapeutics

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The Birth of RNAi

The Nobel Prize for the discovery that double-stranded RNAs (dsRNAs) can trigger silencing of complementary messenger RNA sequences was awarded in 1998, and the term 'RNA interference' (RNAi) was born. This discovery opened the door to a completely novel and untapped market within the pharmaceutical industry.

Shortly thereafter, short dsRNAs — or short interfering RNAs (siRNAs) — were generated artificially and used to demonstrate that this process also occurs in mammalian cells. The knowledge that small strands of RNAs can affect gene expression has had a tremendous impact on basic and applied research, and RNAi is currently one of the most promising new approaches for disease therapy.

In 2004, only six years after the discovery of RNAi, the first siRNA-based human therapeutics — developed to treat wet age-related macular degeneration — entered phase I clinical trials. RNAi is one of the fastest advancing fields in biology, and the flow of discovery gives true meaning to the expression 'from the bench to the bedside'.

New Ideas for RNAi Therapeutics

Although there are still challenges, real strides towards realizing RNAi therapeutics for a wide range of diseases have been made. There are a host of reasons for optimism about the future of RNAi therapeutics and much has been accomplished in the race to bring this new treatment modality to the clinic. Ultimately, successful RNAi-based therapies for life-threatening or debilitating diseases will require the use of targeted delivery strategies that permit systemic delivery. Widespread interest in this phenomenon ensures that we will soon witness fast advances and new applications for RNAi-based therapies. Given the way RNAi has transformed basic research, and the speed with which it has reached the clinic, the coming years promise to be exciting. Ideas with world-changing potential might not be easy to realize, but people do it every day.

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Current siRNA-Targeting Strategies

For new technology, siRNAs have moved into the clinic at an unprecedented pace. Some examples of the diseases and siRNA-targeting strategies currently under investigation are described below.

Drug Candidate	Company	Pharmacological Activity	Indication	Phase of Development
Sirna-027	Sirna Therapeutics/ Allergan	Downregulation of VEGFR1 expression	Wet Age-Related Macular Degenerationt	I
ALN-VSP	Alnylam Pharmaceuticals	Downregulation of kinesin spindle protein (KSP) and VEGF expression	Liver Cancers	
ALN-TTR01	Alnylam Pharmaceuticals	Downregulation of Transthyretin (TTR) expression	Transthyretin (TTR) Mediated Amyloidosis	I
ISIS-CRPRx	ISIS Pharmaceuticals	Downregulation of CRP expression	Cardiovascular Disease	I
ISIS-APOCIIIRx	ISIS Pharmaceuticals	Downregulation of APOCIII expression	Cardiovascular Disease	I
ISIS-FXIRx	ISIS Pharmaceuticals	Downregulation of Factor XI expression	Cardiovascular Disease	I
ISIS-SGLT2Rx	ISIS Pharmaceuticals	Downregulation of SGLT2 expression	Diabetes	I
TD101	TransDerm	Downregulation keratin 6a (K6a) N171K mutant expression	Pachyonychia Congenita	I
pbi-shSTMN1 LP	Gradalis	Downregulation of stathmin-1 expression	Solid Tumours	I
EZN-2968	Santaris Pharma / Enzon Pharmaceuticals	Downregulation of HIF-1 expression	Solid Tumours	I
EZN-3042	Santaris Pharma / Enzon Pharmaceuticals	Downregulation of survivin expression	Cancer	I
CALAA-01	Calando Pharmaceuticals	Downregulation of RRM2	Solid Tumours	I
ALN-RSV01	Alnylam Pharmaceuticals	Downregulation of Respiratory Syncytial Virus's Nucleocapsid 'N' expression	Respiratory Syncytial Virus Infection	II
PF-655	Quark Pharmaceuticals/ Pfizer	Downregulation of RTP801 expression.	Diabetic Macular Edema; Wet Age-Related Macular Degeneration	II
QPI-1002	Quark Pharmaceuticals/ Novartis	Downregulation of protein p53 expression	Acute Kidney Injury	II
Miravirsen	Santaris Pharma	Downregulation of miR-122 expression	Hepatitis C	II
Mipomersen	ISIS Pharmaceuticals	Downregulation of apoB-100 expression	Homozygous Familial Hypercholesterolemia	III
Bevasiranib	OPKO Health	Downregulation of VEGF expression	Wet Age-Related Macular Degeneration	III

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Challenges

Although much is known about the mechanisms of RNAi, applications of this gene-silencing technology need to overcome a number of challenges. For one, RNAi is a fundamentally important regulatory mechanism in the cell, and tapping into it in the interests of therapeutic benefit could result in specific off-target effects. In addition, some synthetic siRNAs can induce general pro-inflammatory off-target effects.

Successful cell-specific delivery *in vivo* is clearly a crucial challenge for achieving the desired RNAi effect in clinical development. As with any other pharmacological treatment modality, therapeutic applications of siRNAs also require effective delivery to target cells and tissues. Most of the pending therapeutic applications based on RNAi rely on direct introduction of synthetic siRNAs to increase cellular uptake. The two main strategies are: delivery of chemically synthesized siRNAs (non-viral delivery), and delivery of shRNA-encoding genes by engineered viruses that will ultimately generate siRNAs by transcription within the target cells (viral delivery).

Until recently, most approaches to *in vivo* delivery have targeted local sites, such as the eye or lungs. Recent progress in the delivery of synthetic siRNAs to specific cell types *in vivo* strongly suggests that RNAi could potentially be used in the systemic treatment of a variety of diseases, including cancer, viral infections, autoimmune diseases, and neurodegenerative diseases.

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QPS is Committed to Working with You

QPS has extensive experience supporting RNAi therapeutic product development, and we truly understand its complexities, in particular to the development of new (imaging) methods, such as quantitative whole-body autoradiography (QWBA) and microautoradiography (MARG) to monitor the *in vivo* biodistribution of siRNAs at the organ, tissue, and cellular level. In combination with rt-PCR, the up or down regulation of specific genes can be monitored at the tissue level. Furthermore, this can be coupled to PK sample analysis via hybridization-ELISA or LC-MS/MS for PK/PD correlation. We are committed to working with you to advance your RNAi product portfolio in this rapidly developing market segment, for the benefit of patients worldwide.

Broad Strategic Access

QPS provides clients with broad strategic access to its nonclinical and clinical development capabilities, as well as its experience in conducting nonclinical and clinical development of a diverse portfolio of siRNAs across various therapeutic areas. Our preferred vendor agreements also provide for the establishment of a client-dedicated unit within our organization.

Timely Delivery

Partnering with QPS will position you to succeed in the timely delivery of your RNAi products to the marketplace.

References

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Utilizing RNA interference to enhance cancer drug discovery Nature Reviews Drug Discovery 2007; 6: 556-568.
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