Citation: Molecular Therapy–Nucleic Acids (2012) 2, e8; doi:10.1038/mtna.2011.9

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COMMENTARY

The Business of RNAi Therapeutics in 2012

Dirk Haussecker[1]

Molecular Therapy–Nucleic Acids (2012) **2**, e8; doi:10.1038/mtna.2011.9; published online 7 February 2012

INTRODUCTION

In its decade in existence, commercial RNA interference (RNAi) therapeutics development has seen great financial volatility. The causes of this volatility are broadly shared with what has been observed on other technology frontiers such as gene therapy in the case of drug development, with the amplitude of the volatility magnified or moderated by macroeconomic factors. Volatility poses challenges especially for financially exposed small biotechnology companies, the core translational force of the industry, to establish the platform and develop drugs in a process that takes at least 15 years to bear fruits in the form of approved drugs and depends on the complex interactions between a diverse set of investors. Even small disruptions can have big repercussions leading to both euphoria and capitulation which can be equally damaging to the long-term health of a sector.

This commentary is directed at companies already involved in RNAi therapeutics development or those interested in entering the space. By analyzing the forces that shape the business of RNAi therapeutics at the start of 2012 it aims to uncover key opportunities for value creation. It may also help investors identify related investment opportunities and inventors commercialize their intellectual property (IP). For a review of the fundamental business case for RNAi therapeutics, the reader is referred to an earlier article on the topic.[1]

RNAi THERAPEUTICS BUSINESS TRENDS IN HISTORICAL PERSPECTIVE

The business of RNAi therapeutics has just entered its fourth phase. The first, discovery phase (2002–05) was defined by the early adopters of RNAi as a therapeutic modality following the discovery of RNAi in human cells.[2] These were small, risk-taking biotechnology companies such as Ribozyme Pharmaceuticals (aka Sirna Therapeutics), Atugen (aka Silence Therapeutics) and Protiva (aka Tekmira). As much as they may have believed in the potential of RNAi therapeutics, their strategic reorientation was also a gamble on a technology with considerable technical uncertainties in order to turn around declining business fortunes by leveraging their nucleic acid therapeutics know-how to become leaders in a potentially disruptive technology. For example, exploration of *in vivo* gene knockdown had only just begun, not to speak of knockdown in larger animals following systemic delivery. This phase also saw the founding of Alnylam Pharmaceutical based on the idea of cornering the IP on the molecules that mediate RNAi (RNAi triggers) so that it may finance its own drug development by collecting a toll from all those engaged in RNAi therapeutics.

Until then, larger pharmaceutical companies ("Big Pharma") saw the value of RNAi largely as a research tool only. This, however, changed quickly when a few of them, including Medtronic, Novartis, and Merck, were seen by their peers to take an interest in RNAi as a therapeutic modality. The situation seemed reminiscent of monoclonal antibodies which had just established themselves as the major value creator in the pharmaceutical industry, but where Big Pharma was thought to be paying the price for having watched from the sidelines for too long. Another factor for Big Pharma's surging RNAi therapeutics interest, the defining feature of the second, boom phase of RNAi therapeutics (2005–08), was the impending patent cliff and the hope that the technology would mature in time to soften its financial impact.

A bidding war, largely for access to potentially gatekeeping RNAi trigger IP erupted. Most notably, Merck and Roche paid US$1.1B for acquiring Sirna Therapeutics and US$300M+ for a limited platform license from Alnylam, respectively. These deals were only rivaled in attention by the award of a Nobel Prize to Andrew Fire and Craig Mello for their seminal discovery of double-stranded RNA (dsRNA) as the trigger of RNAi. The industry naturally did not mind the attention and in some cases fanned the fire by raising unrealistic expectations. This atmosphere also gave rise to controversial publications in high-profile journals which lent credence to the mistaken notion that the technical barriers to exploiting the RNAi trigger IP would be low.[3,4] Consequently, most Big Pharma companies had a stake in the technology. Yet, the US$2.5B–3.5B in investments largely failed to formulate sound strategies for the real technical challenges such as delivery. Symptomatic for the times, the financial markets similarly failed to realize the value of truly enabling technologies: in the 2 weeks following the publication of a seminal paper on systemic small interfering RNA (siRNA) delivery by Protiva (now Tekmira) and Alnylam on 26 March 2006,[5] Alnylam's share price would decline by over 10%.

It is therefore perhaps not surprising that this period of high expectations and blockbuster deals was followed by general

[1]Department of Medical Biotechnology, College of Natural Sciences, Dongguk University, Seoul, Korea
Correspondence: Dirk Haussecker, Department of Medical Biotechnology, College of Natural Sciences, Dongguk University, 26, Pil-dong 3, Jung-gu, Seoul 100-715, Korea.
E-mail: dirk.haussecker@gmail.com

backlash (2008–2011), the financial consequences of which were exacerbated by global economic turmoil and healthcare rationing in the West. Big Pharma quickly realized their mistake of putting IP before enablement as they scrambled to scout for delivery technologies and found the majority of them not to live up to their claims.[6] Roche, a year after their IP license from Alnylam, felt compelled to pay US$125M for Dynamic PolyConjugates from Mirus Bio, one of the more promising and differentiated delivery technologies, for which, however, significant risks related to translation into organisms beyond rodents and manufacturing/scale-up remained. Contributing to buyer's remorse was the ageing and rapidly eroding gate-keeping potential of the RNAi trigger IP that had been the focus of their original investments.

As much as delivery, it was the potential of certain RNAi formulations to stimulate innate immunity that caused much of the scientific angst that contributed to the deteriorating business sentiment in 2008.[7,8] It almost came to be assumed that an *in vivo* RNAi efficacy claim was in fact an innate immunostimulatory artefact. Importantly, this suspicion extended to the preclinical data that formed the rationale for the industry's lead clinical candidates in wet age-related macular edema (Acuity/Opko's Cand5, Merck/Allergan's Sirna-027/AGN-745, Quark/Pfizer's PF-4523655)[9,10] and respiratory viral infection (Alnylam's ALN-RSV01),[11] approaches which incidentally did not involve specific delivery chemistries. Making matters worse still, innate immune stimulation is a safety issue. Although today innate immunostimulatory potential is widely considered to be manageable through chemical modification and choice of RNAi trigger structure, the reputational damage persists.

Suffering from RNAi-specific scientific and credibility issues and with first drug approvals still years away, RNAi therapeutics was among the first to feel the cost-cutting axe at companies like Pfizer, Merck, Abbott Labs, and Roche which all started to suffer from patent expirations, drug approval and productivity issues, worsening drug reimbursement climates, and the general loss of confidence in their innovative abilities. Particularly the exit of Roche from in-house RNAi therapeutics development sent shockwaves through the industry. Having invested heavily in the technology only 2–3 years ago and being considered an innovation bellwether within Big Pharma, Roche's decision in late 2010 found a number of imitators among Big Pharma and has been functioning as a major barrier to new investments in RNAi therapeutics.

The backlash, however, also had cleansing effects which form the basis for the 4th, recovery phase of RNAi therapeutics (2011–present). As a result of the financial restrictions and increased scientific scrutiny, there has been an overall increase in the quality of the science. RNAi therapeutics has also become less of a target for the quick-rich biotech schemes that constantly chase the next hot area in drug development. This quality shift is most evident in the evolution of the RNAi therapeutics clinical pipeline which has become more and more populated with candidates based on sound scientific rationales, especially in terms of delivery approaches and anti-immunostimulatory strategies. For the recovery, however, to firmly take root and for the long-term health of the industry, it is important for the current clinical dataflow to bring back investors.

RNAi THERAPEUTICS ASSETS

One measure for the health of an industry is in accounting its assets. These are also at the center of business activity. Because drugs are the ultimate objective of RNAi therapeutics and because of the significant de-risking that occurs during drug development, the clinical and late-stage preclinical pipeline weighs heavy. Equally important at this relatively early stage are the technologies that enable candidate development and drive platform efficiencies. These technologies need to be protected by patents or trade secrets for individual companies to capture their full value.

RNAi therapeutics development pipeline. As of the 2008 review,[1] there were eight candidates in clinical development (**Table 1**). What is noticeable is that most of them were local RNAi approaches that today would most likely not enter development due to uncertain scientific rationale or safety: naked delivery, in some cases with unmodified synthetic RNAi triggers (Cand5, Sirna-027, RTP-801i, ALN-RSV01, TD-101), liposomal delivery of a DNA-directed RNAi (ddRNAi) candidate which could have been predicted to be inadequate for antiviral applications and was all but assured to cause immune stimulation (NucB1000),[12] or first-generation ddRNAi expression systems subsequently[13] found to frequently cause cellular toxicity (rHIV-shI-TAR-CCR5RZ; possibly NucB1000). Not surprisingly, many of these programs were either terminated, or their future development is doubtful. Among the latter, there is hope that Quark/Pfizer's PF-4523655 and Alnylam's ALN-RSV01 can still make it to market as long as they show appropriate safety and efficacy even though their value to RNAi therapeutics would be limited given the widespread skepticism about their mechanism of action.

Since 2008, the development pipeline has not only grown in size (18 active clinical candidates today), but more importantly it has improved in quality concomitant with a shift from local to systemic delivery: 7 of the 14 new clinical candidates since 2008 were delivered systemically, compared to only 1 of the 8 before. This is largely the result of the clinical entry of the most advanced systemic delivery platforms, stable nucleic acid lipid particles (SNALP) and AtuPLEX. SNALP alone accounts for six clinical candidates (ALN-VSP02, TKM-ApoB, ALN-TTR01, TKM-PLK1, ALN-PCS02, TKM-EBOLA) and one more is expected to enter the clinic in the near future (ALN-TTR02).

Given that the value of a given drug candidate is dynamic and can dramatically change with each new data point—such as a clinical trial result or even change in regulatory policy—it is beyond the scope of this commentary to determine the market value of the RNAi development pipeline. Some candidates, however, have been licensed which makes their market value easier to assess. Quark Pharmaceuticals for example has been quite successful in licensing its compounds. As of 31 December 2010, Pfizer had invested $52.5M in PF-4523655 which is in late phase II development for wet age-related macular edema and diabetic macular edema. Quark moreover is eligible to receive substantial future milestones and royalties.[14] Still, the value of PF-4523655 has become highly uncertain after phase II study results suggested that PF-4523655 faces an uphill battle before it can be a commercially viable drug.

Table 1 RNAi therapeutics clinical pipeline

Year of IND/CTA	*Candidate*	*Indication*	*Target*	*Delivery*
2004	Cand5	Wet AMD, diabetic macular edema	VEGF	Intravitreal needle injection (retina; local)
2004	Sirna-027/AGN-745	Wet AMD	VEGF-R1	Intravitreal needle injection (retina; local)
2005	ALN-RSV01	RSV infection	Viral RNA	Inhalation of unformulated siRNAs (lung epithelium; local)
2007	DGFi	Acute kidney injury, delayed graft function	p53	Intravenous naked siRNA (proximal tubule cells; systemic)
2007	PF-4523655	Wet AMD, diabetic macular edema	RTP801/REDD1	Intravitreal needle injection (retina; local)
2007	rHIV-shl-TAR-CCR5RZ	HIV infection	Viral RNA and host factors	Lentiviral (hematopoietic stem cells; *ex vivo*)
2007	NucB1000	Hepatitis B viral infection	HBV RNAs	Liposomal plasmid (hepatocytes; systemic)
2008	TD101	Pachyonychia congenita	Mutant keratin	Intradermal needle injection (skin; local)
2008	Therapeutic vaccine	Metastatic melanoma	Immunoproteasome	Electroporation (autologous monocytes; *ex vivo*)
2008	Excellair	Asthma	Syk kinase	Inhalation of unformulated siRNAs (lung epithelium; local)
2008	CALAA-01	Nonresectable or metastatic solid tumors	M2 subunit of ribonucleotide reductase	RONDEL (solid tumor cells; systemic)
2008	ALN-VSP02	Liver cancer, cancer with liver involvement	VEGF, KSP	SNALP liposome (hepatocytes; systemic)
2009	Atu027	Advanced solid tumors	PKN3	AtuPLEX lipoplex (vascular endothelial cells; systemic)
2009	QPI-1007	Chronic nerve atrophy, nonarteritic ischemic optic neuropathy	Caspase 2	Intravitreal needle injection
2009	SYL040012	Intraocular pressure and glaucoma	β-Adrenergic receptor 2	Eye drop (ciliary epithelial cells; local)
2009	TKM-ApoB	Hypercholesterolemia	Apolipoprotein B	SNALP liposome (hepatocytes; systemic)
2009	bi-shRNAfurin/GMCSF	Ovarian cancer, advanced melanoma	Furin	Electroporation plasmid (autologous tumor samples; *ex vivo*)
2009	ALN-TTR01	Transthyretin amyloidosis	Transthyretin	SNALP liposome (hepatocytes; systemic)
2010	siG12D LODER	Operable pancreatic ductal adenocarcinoma	Mutated KRAS	LODER local drug elution
2010	TKM-PLK1	Solid cancers and lymphoma	Polo-like kinase 1	SNALP liposomal (solid tumor cells; systemic)
2011	CEQ508	Familial adenomatous polyposis/colon cancer prevention	-Catenin	Bacterial (mucosal layer of small and large intestine; oral)
2011	ALN-PCS02	Hypercholesterolemia	PCSK9	SNALP liposome (hepatocytes; systemic)
2011	TKM-EBOLA	Ebola infection (biodefense)	Viral RNA	SNALP liposome (hepatocytes and phagocytes; systemic)
Select preclinical candidates				
2012 (est.)	RXI-109	Dermal scarring	CTGF	Intradermal needle injection (skin; local)
2012 (est.)	To be named	HIV infection	CCR5	Lentiviral transduction transduction (hematopoietic stem cells; *ex vivo*)

Abbreviations: AMD, age-related macular edema; CTGF, connective tissue growth factor; GMCSF, granulocyte-macrophage colony-stimulating factor; HBV, hepatitis B virus; KSP, kinesin spindle protein; PKN3, protein kinase N3; RSV, respiratory syncytial virus; shRNA, small hairpin RNA; siRNA, small interfering RNA; SNALP, stable nucleic acid lipid particles; VEGF, vascular endothelial growth factor.

Quark also sold an option for an exclusive license to its second-most advanced candidate, QPI-1002, then in phase I for acute kidney injury and delayed graft function, for a remarkable US$10M fee to Novartis. The market value of the only other partnered candidate in clinical development, ALN-RSV01, has decreased considerably as its target population has shrunk drastically and after Alnylam's partners for this drug candidate, Kyowa Hakko and Cubist Pharmaceuticals, have distanced themselves from it despite having invested more than US$35M in upfront alone.

The remaining value of the clinical pipeline largely rests on three oncology candidates (ALN-VSP, Atu027, TKM-PLK1) and the SNALP-enabled ALN-PCS02 for hypercholesterolemia and ALN-TTR01/02 for transthyretin amyloidosis. This judgment is based on delivery that has been de-risked to some extent for these candidates, almost nonexistent target risks for three of them (TTR, PLK1, PCS02), and the fact that they all represent highly differentiated approaches for diseases of considerable unmet medical needs. Moreover, there exist early biomarker opportunities for two of them (TTR, PCS). Should these biomarker read-outs demonstrate effective target gene knockdown in their phase I studies, their value would increase considerably, possibly pegging their upfront partnering value in the high double-digit millions with

the potential to generate substantially more revenues downstream. In the case of ALN-VSP and Atu027, early clinical data are already supportive of further development with the sponsors hoping to license these compounds in 2012.

Although having only just entered clinical development, TKM-EBOLA may actually be the pipeline asset with the highest net present value in the industry. This is because the full development of this biodefense candidate is being funded under a US$140M contract from the US Department of Defense. This contract allows Tekmira to not only earn incentive fees and profit from eventual stockpiling contracts, but also to develop the candidate in a way that broadly benefits the platform on which it was built. Among the other preclinical pipeline candidates, RXi Pharmaceutical's RXI-109 for dermal scarring, and Calimmune's ddRNAi candidate for HIV deserve special mention based on their promising preclinical results,[15] differentiation, and potential to blaze the trail for their respective self-delivering rxRNA and lentiviral ddRNAi platforms.

Enabling technologies. As indicated by the evolution of the RNAi therapeutics product pipeline, it is the underlying technologies, foremost delivery, that are the major value drivers. Other technologies, however, also add value by reducing adverse event risk, and in the case of RNAi trigger innovation by opening up new therapeutic frontiers.

Delivery: one cell/tissue type, many indications. The present expansion of the SNALP-based pipeline reflects a fundamental principle of RNAi therapeutics: once a delivery technology is found suitable for knocking down genes in a given cell/tissue type, any gene can be targeted in that cell/tissue type with the possible applications only limited by our exploding understanding of disease genetics (**Table 2**). SNALP, Tekmira's PEG-stabilized monolamellar liposomes that encapsulate the RNAi trigger payload in its aqueous interior and which are neutrally charged at physiologic pH, is furthest developed for knocking down genes expressed in the liver, particularly hepatocytes.[5] Solid tumor cells,[16] sites of tissue inflammation, and phagocytic cells,[17] however, are also suitable targets for SNALP due to their relative accessibility and/or natural propensity to take up nanosized particles.

With the caveat that there is sequence-dependent variability, results from the SNALP-based trials with TKM-ApoB and ALN-VSP02 suggest that the SNALP formulations that were developed initially have potential for a few indications with less stringent tolerability and cost requirements. Improvements in the efficacy and tolerability of SNALP over the last 5 years,[18] however, have significantly widened applicability through an expected 100- to 1,000-fold improvement in the therapeutic index, and further enhanced the competitive profile of SNALP by reducing cost and treatment frequencies.

Symbolizing the value shift from RNAi triggers to delivery, Alnylam, which once relied on its RNAi trigger IP for its industry-leading position, has been sued by Tekmira for scheming to unlawfully gain control and ownership over SNALP technology and otherwise causing damage to Tekmira's competitive position. Somewhat benefitting from this gridlock in SNALP is the industry's second-most advanced systemic delivery technology, AtuPLEX by Silence Therapeutics. This multilamellar, positively charged, lipid-based formulation has proven useful for knocking down genes in the vascular endothelium in small and large animal models.[19] The pharmacokinetic and safety data that emerges from the ongoing Atu027 trial (e.g., ASCO 2011 poster presentation) indicate this also likely to be the case in humans. With applications particularly in oncology (antiangiogenesis) and acute inflammatory conditions (the vascular endothelium as a barrier to inflammatory cell infiltration), this technology has garnered increased partnership interest. Positively charged lipoplexes, in this case delivered by intravesical instillation, may also be useful for knocking down genes in the superficial layers of the bladder, including malignancies, as suggested by preclinical data from Marina Biotech.[20]

Besides these and other lipid-based delivery technologies, there are a number of polymer and conjugate delivery technologies in earlier development. What started with largely negatively charged RNAi triggers complexed to positively charged polymers, an approach frequently associated with toxicities,[21] polymers appear to be more promising as neutrally charged polyconjugates.[22] Especially the smaller conjugates may be suited for gene knockdown in tissues not accessible to the larger lipid-based formulations. Manufacturing challenges and biodegradability issues, however, could be causing delays in their clinical translation. This appears to be the case for the Dynamic PolyConjugates for which Roche paid US$125M in 2008, but which Arrowhead Research recently acquired for single-digit million US dollars.[23]

Smaller than polyconjugates, simple conjugates such as the GalNAc-siRNAs (target organ: liver) developed by Alnylam may similarly reach a wider range of target cells/tissues and could also be amenable to subcutaneous administration. Potency improvements, however, are required to render them competitive with the more complex formulations for systemic applications when the target cell/tissue is shared. It is in local/localized applications that similar small conjugates currently have most utility. A first such program is about to enter clinical development with RXi Pharmaceutical's intradermally injected self-delivering rx-RNA RXI-109 for dermal scarring. Ocular, central nervous system (intraparenchymal, intrathecal) and respiratory (epithelial) applications may similarly benefit from simple conjugate solutions.

The RNAi trigger versus delivery debate is more balanced in ddRNAi technology. This is because delivery technologies can be directly borrowed from the field of gene therapy, with particularly adeno-associated virus and lentiviral delivery

Table 2 Tissues/cell types amenable to therapeutic RNAi today

Tissue/Cell type	*Delivery*
Liver (hepatocytes, but also other cell types)	SNALP
Vascular endothelial cells	AtuPLEX
Solid tumor cells	SNALP
Phagocytic cells, including antigen presenting cells	SNALP
Skin	Self-delivering rxRNAs
Hematopoietic stem cells	Lentivirus
CNS, eye	AAV, lentivirus

Abbreviations: AAV, adeno-associated virus; CNS, central nervous system; RNAi, RNA interference; SNALP, stable nucleic acid lipid particles.

well suited for a number of central nervous system,[24] ocular,[25] and hematopoietic stem cell-related applications.[15] Conversely, because ddRNAi is intended for gene silencing over extended periods of time following a single administration, and adverse reactions due to ddRNAi trigger activity cannot easily be reversed, ddRNAi trigger safety is paramount.[13]

Some of the delivery technologies above can also be used for *ex vivo* delivery. Here, the delivery challenge is essentially reduced to a tissue culture problem by RNAi treating the target cells outside the body using transfection, electroporation, or viral transduction, before (re-)introducing them into the patient. This approach holds particular promise for stem cell-based therapeutics[15] and therapeutic cancer vaccines.[26]

In summary, albeit delivery technologies of clinical and commercial maturity are still relatively few in number, today's delivery capabilities already allow for a number of high-quality RNAi therapeutics opportunities. This is because each delivery technology, once found to be suitable for gene knockdown in a given cell/tissue type, can be rapidly expanded to many target genes and applications. Control over and access to these technologies is critical for RNAi therapeutics platform success.

RNAi triggers: potency matters, but value also in safety and new functionalities. One of the main developments in the RNAi trigger field has been the realization that many RNAs with dsRNA elements can induce RNAi gene silencing at least to some degree.[27] Together with the weakening of Alnylam's RNAi trigger IP estate in the course of the Kreutzer–Limmer (KL) and Tuschl patent prosecutions, choice and access to RNAi triggers has become less rate-limiting than it was once thought of. It also means that working around somebody else's IP estate alone does not easily compensate for deficiencies in scientific performance, especially knockdown potency which normally determines both the maximal degree and duration of the knockdown. Consequently, non-Tuschl RNAi triggers should be at least equal in potency, if not superior, or offer additional advantages in safety and functionality.

In terms of potency, a single asymmetric instead of symmetrical 3′ overhangs on the guide strand has been found to improve on the knockdown efficacy of Tuschl siRNAs.[28] Potency can also be improved by applying thermodynamic design rules such as the Zamore rules to which Silence Therapeutics has an exclusive license.[29] Although the Dicer-substrate RNAi triggers had once been proposed not only to fall outside of Alnylam's RNAi trigger patent estate, but also to be more potent than Tuschl siRNAs,[30] they may actually be a more appropriate example for the value of functional differentiation by facilitating certain delivery strategies[31] and potentially also by extending the duration of gene silencing.[32]

Synthetic small hairpin RNAs can either function as Dicer-substrate RNAs or also be smaller in size, yet still trigger RNAi (e.g., SomaGenics).[32] These single-molecule RNAs have the benefit of increased thermodynamic stability which may be exploited for the manufacture of RNAi triggers with increased dsRNA yield than conventional two-stranded siRNAs[33] as well as delivery approaches which require single-stranded phases during the delivery journey. Shorter small hairpin RNAs should also be less prone to induce innate immunity and interfere with endogenous small RNA processing. The latter attributes also apply to the first-generation asymmetric siRNAs (asiRNA) by Biomolecular Therapeutics which are characterized by shorter double-stranded elements than those in conventional siRNAs.[34] RXi Pharmaceutical's sd-rxRNAs have even shorter double-stranded elements, a feature the company claims to be critical for crossing hydrophobic lipid bilayers during delivery. Nevertheless, because the success rate of finding potent RNAi triggers may drop noticeably for RNAi triggers with such short dsRNA elements, these structures should be preferentially contemplated in applications where they can add unique delivery or safety benefits.

The structural flexibility of RNAi triggers has also been exploited for increased functionality by having them target more than one gene ("multitargeting"). This is particularly valuable for treating complex diseases or where resistance is an issue (cancer, viral infections). Multitargeting is already being pursued in ALN-VSP02 and Tekmira's Ebola program which involve the inclusion of several conventional siRNAs in a given formulation,[16] but it can also be achieved for example by using three- or four-stranded designs, both Dicer-substrate and non Dicer-substrate, in which the individual strands guide the cleavage of distinct targets.[35] Tekmira has recently licensed a three-stranded RNAi trigger design from Halo-Bio.

Although certainly adding to functionality, two RNAi trigger structures exploiting RNAi trigger structural diversity, immunostimulatory siRNAs (e.g., Alnylam)[36] and single-stranded RNAi triggers (e.g., ISIS Pharmaceuticals)[37] run counter to two core principles of RNAi in Man. First, it was the Nobel-Prize winning insight by Fire and Mello that dsRNA, and not for example single-stranded antisense RNA, is the trigger in RNAi. Second, the discovery of RNAi in mammals was based on the use of shorter dsRNAs that would not stimulate the nonspecific interferon response. It therefore remains to be seen whether the potency disadvantage (single-stranded RNAi) and safety liability (immunostimulatory siRNAs) of these triggers can be compensated for by their unique delivery attributes (single-stranded RNAi) or any anticancer, antiviral, or antiangiogenic effect of immunostimulatory siRNAs.

Unlike in synthetic RNAi triggers, innovation in ddRNAi trigger design has somewhat stalled, particularly in the commercial and translational arenas, with most groups still employing first-generation minimal small hairpin RNAs driven by U6 and H1 Pol-III promoters. With safety remaining a concern for these systems,[13] and the causes of toxicity still to be fully identified, there is considerable value to be created by establishing alternative ddRNAi expression systems.

Tools to minimize RNAi-related adverse event risk. The challenges of drug development do not stop with hitting the target. In a risk-averse regulatory environment, even theorized or minor safety signals in preclinical studies can lead to substantial delays in the approval process. The value of technologies that minimize adverse event risk is therefore not only in protecting patient safety, but also in avoiding regulatory surprises. In RNAi therapeutics, such technologies can be categorized into those that address acute toxicity and those that deal with the risks associated with their long-term use.

Acute immune responses from activating innate immune receptors or the complement system is commonly considered

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