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COMMENTARY

The Business of RNAi Therapeutics in 2012

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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

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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-shI-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	βCatenin	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

the next biggest scientific challenge besides delivery.[8] Indeed, RNAi-related "flu-like symptoms" with inflammatory cytokine elevations have been observed in a number of clinical trials (e.g., TKM-ApoB, NucB1000, CALAA-01),[12] and activation of the alternative complement pathway was seen in the Atu027 trial. Although the clinical importance of such observations can vary considerably, it is necessary to improve on that record. Fortunately, understanding and mitigating, if not abolishing acute immune responses has been one of the most fertile areas of RNAi therapeutics research in recent years. We now understand most of the relevant nucleic acid structural parameters (e.g., dsRNA length, GU-rich elements) and chemical modifications (e.g., 5′-triphosphates, 2′-O-methyl), as well as the innate immune receptors (TLR3, 7, 8; RIG-I; PKR) and cell types by which such activation may occur. Consequently, it is possible to adjust the RNAi trigger structure and, in the case of synthetic RNAi triggers, apply chemical modifications to minimize acute immune stimulation risk, a prediction which can then be tested in predictive assays.[38] While capitalizing on this progress by licensing related IP has proven difficult, companies like Tekmira have created brand value by establishing themselves as early adopters and experts in this area.[8]

Adverse side-effects stemming from the ability of siRNAs to function as microRNAs by dampening the expression of often hundreds of off-target genes is a safety concern especially in administering an RNAi therapeutic over extended periods of time (microRNA-type off-targeting).[39] Similar to innate immune stimulation, progress in tackling this technical challenge has been swift over the last 5 years. Approaches to minimizing such off-targeting include bioinformatics which considers potential interactions between the seed element of an siRNA with the genome-wide repertoire of 3′-UTRs during the *in silico* stage of RNAi trigger selection, as well as chemical and structural modifications that can essentially eliminate passenger strand-mediated off-targeting (e.g., by passenger strand 5′ blocking or by shortening the length of the passenger strand)[34,40] and considerably reduce guide strand-mediated off-targeting by penalizing seed-only interactions of a guide strand without compromising its ability to recognize (on-)targets via more extensive base-pairing (e.g., by including 2′-O-methyl, unlocked nucleic acid-modifications in the seed).[41,42] With the help of standard genome-wide expression tools, the effect of these strategies can now be routinely assessed and demonstrate that substantial reductions in off-targeting can be achieved by implementing the above strategies.[42]

It should be added, however, that although such advanced technology tools for minimizing microRNA-type off-targeting exist and bioinformatic approaches are widely applied at the *in silico* stage of the RNAi trigger selection, the practical part of the RNAi selection and optimization process is still dominated by potency and the abrogation of immune stimulation. This is partly also due to the difficulty of interpreting what the modulation of dozens of off-target genes means in toxicological terms, and maybe also a concern that too much information, for example theoretical concerns arising from expression changes of a gene that has been linked to cancer, could cause delays in a risk-averse regulatory climate. Of note, genome-wide off-targeting has received much less attention in the older antisense therapeutics field despite it being of equal importance to that field.

Toxicity due to interference with the functions of endogenous gene silencing as a result of competition for shared factors is another type of potential toxicity that is more likely to manifest itself over the long-term than at the time that the RNAi therapeutic is administered. This type of toxicity is mostly a concern for strategies that harness the endogenous RNAi/microRNA pathway upstream of RNA-induced silencing complex (e.g., synthetic Dicer-substrates, most ddRNAi approaches),[13] although perturbations due to competition have been detected by sensitive gene expression analysis with siRNAs, too.[43] Currently, the best strategy to avoid such complications is to not use excessive amounts of RNAi triggers and by applying "gentle" designs that promote their efficient processing. Recent progress in the enzymology of particularly Dicer processing[44] and RNA-induced silencing complex loading[45] provide guidelines for this.

In summary, advances in a range of enabling technologies have greatly enhanced the quality of RNAi therapeutics science since 2008. This is in contrast to, and indeed was possibly encouraged by the recent criticisms of RNAi therapeutics.

IP, know-how, and trade secrets. The value that individual companies can derive from the above enabling technologies also depends on their ability to protect them by patents, also for licensing purposes, or on keeping them as trade secrets, thus maintaining their competitive advantage in areas that are critical for RNAi success and require deep technical know-how. Because basic RNAi trigger structures are easily reverse engineered and are prone to inadvertent disclosure, seeking patent protection is a common strategy in RNAi triggers. One of the biggest changes in the strategic landscape in (synthetic) RNAi therapeutics since 2008 has been the disappearance of RNAi trigger IP with gate-keeping potential (**Table 3**). This is largely the result of the course the KL (claiming dsRNAs of wide size range) and Tuschl patent prosecutions (claiming the sweet-spot of dsRNA length and the 3′ overhang feature) have taken in the United States and Europe: the Tuschl I and KL patents are likely to be limited to therapeutically irrelevant methods of generating RNAi triggers (e.g., isolated RNA from enzymatic processing reactions in cell lysates-Tuschl I) or to structures of little potency (e.g., short dsRNAs held together by covalent chemical linkage-KL). Only the Tuschl II patent family continues to look strong in regards to one of the most desirable RNAi trigger structures, 19–21 bp dsRNAs with 3′ overhangs. Similarly, the Zamore patent series, recently challenged and upheld in the United States, broadly covers an influential design feature (differential thermodynamic end-stability), especially in Europe. Nevertheless, in both cases scientifically acceptable workarounds are available and their value primarily resides in maximizing RNAi trigger choice and reducing discovery cost. The disappearance of potentially gate-keeping RNAi trigger patents also had the effect of reducing the value of RNAi triggers for which the primary motivation had been to provide KL/Tuschl workaround solutions.

The situation is different in ddRNAi therapeutics where following the apparent destruction of fundamental ddRNAi trigger IP as a result of the Benitec–Nucleonics conflict,

Table 3 Changes in strategic RNAi trigger IP landscape since 2008

Patent family	*Potential blocking threat 2008*	*Present status*
Fire (US6506559, US7560438)	All dsRNAs, although licensor (Carnegie Institute of Washington) pursued broad non-exclusive licensing strategy	Likely only useful for *ex vivo* delivery approaches
Kreutzer–Limmer (European only: EP1550719, EP1214945)	All dsRNAs from 15–49 bp (all useful RNAi triggers)	Never rose to prominence in US; in Europe, although '945 still potentially broad, K-L series likely to cover only "unusual" structures, such as 15 bp dsRNAs held together by covalent linkage
Tuschl I (US patent app 09/821832, 10/255568; EP1309726)	All dsRNAs ~19–23 bp (sweet-spot of RNAi triggers)	Abandoned (US); limited to therapeutically irrelevant production methods, e.g. fly lysates (Europe)
Tuschl II (US patent app 10/832432, 10/832,248, 10/433050; US7056704, US7078196; EP1407044)	All 3′-overhang siRNAs from ~18–24 bp	European patent still broadly covering valuable 3′ overhang feature, but opposition proceeding ongoing; US patents partly issued, partly examination ongoing; in both cases various objections raised especially in light of "Bass" and "Tuschl I"
Zamore (US US7750144; EP1633890)	RNAi triggers enhanced by seminal thermodynamic end-stability design rule	Very broad claims issued in Europe (opposition filed); US claims useful, but can be worked around; however, presents uncertainty to most modified RNAi triggers
Graham (US6573099; EP1555317)	ddRNAi gate-keeping US patent rejected in re-exam instigated by Nucleonics	Re-issued in US and issued in Europe with claims arguably covering most/all current clinical ddRNAi approaches; potential weakness: limitations in linker sequence as well as length and complementarity of dsRNA

Abbreviations: ddRNAi, DNA-directed RNA interference; dsRNA, double-stranded RNA; IP, intellectual property; RNAi, RNA interference; siRNA, small interfering RNA.

Benitec managed the unusual feat of getting its ddRNAi trigger IP ("Graham patents") widely reinstated in its original strength. However, as with any of the potentially fundamental patent applications covering RNAi triggers, its value is rapidly deteriorating given that the number of ddRNAi therapeutics that still have a chance of reaching commercialization by the time the IP expires (~2018 in the case of Graham) is shrinking rapidly. What makes it difficult for companies to enforce and monetize such IP before drug approval and commercialization is the Research Exemption which gives companies broad protection when utilizing patented matter as long as it is used in the process of obtaining regulatory approval.

This assumption, however, may be put to the test after ISIS Pharmaceuticals recently sued Santaris on RNaseH gapmer technology which ISIS claims to own and Santaris allegedly infringed upon by selling it in the course of their collaborations with Big Pharma. Absent a reinterpretation of the Research Exemption, however, the value of RNAi trigger IP resides increasingly in fresher IP that covers more specific features such as the sequence of the 3′ overhang or thermodynamic design rules which may be scientifically desirable, but not indispensable. Further motivating companies to take licenses to RNAi trigger IP should be the need to ensure freedom-to-operate in a patent landscape that is getting increasingly crowded by a number of narrower patents.

What is sometimes forgotten in the discussion of RNAi trigger-related IP is that with the exception of the latest RNAi trigger inventions, the value of IP related to basic RNAi trigger structures in terms of market exclusivity is limited as RNAi therapeutics offers multiple IP opportunities downstream of the basic RNAi trigger structure which will set the clock for loss of market exclusivity and include the specific RNAi trigger sequence or formulation.

In contrast to RNAi triggers, a much higher portion of the competitive value in delivery is tied up in the form of trade secrets and know-how, the value of which typically scales with the complexity of a delivery technology: simple conjugates rely more on patent protection than difficult-to-formulate nanoparticles. The value of delivery trade secrets is also illustrated by the fact that there has yet to be a generic version of a nanoparticle-based drug.[46] This should be a particularly attractive feature to the pharmaceutical industry which is currently in patent-cliff freefall. The importance of trade secrets and know-how in RNAi therapeutics is exemplified by liposomal delivery where precise formulation ratios, the understanding of rational lipid design, and manufacturing know-how has been the difference between technologies that fail to progress beyond the rodent-stage of development, and those that can be translated further into nonhuman primate and clinical studies. It is this know-how that allowed Tekmira to become a major player in RNAi therapeutics, but which Tekmira claims Alnylam, by taking advantage of its partner status and by inappropriately hiring former Tekmira employees, has violated in a series of deceptive and malicious acts to enrich itself and marginalize Tekmira. On the other hand, the legal case also illustrates the dangers of a trade secret-dependent business model in an industry where partnering is essential, but where partners can often be your fiercest competitor.

BUSINESS DEVELOPMENT STRATEGIES

Small RNAi therapeutics innovator ("pure-play") companies and Big Pharma remain the industry's two protagonists, although medium-sized pharmaceutical companies, including those in Asian countries, have taken some of the space vacated by Big Pharma. The following section analyzes the strategies of pure-play RNAi innovator companies and RNAi asset buyers during the RNAi therapeutics backlash and provides business development suggestions going forward.

The pure-play perspective. The fate/response of first-generation pure-play RNAi therapeutics companies has been as diverse as their technical capabilities and motivations: some closed shop as investors lost faith in their science and business practices (e.g., Nucleonics), while the survivors tried

everything from focusing efforts on the achievement of key technical and product milestones to broadening their technology offerings and merging with each other. Still, they, along with the few new entrants, are united by the hope that should RNAi therapeutics appetite return, for example as a result of the ongoing clinical dataflow, they will be well positioned to ride the wave of renewed enthusiasm. The following section discusses major business development themes in the pure-play RNAi therapeutics space.

Shift from RNAi triggers to delivery. Unsurprisingly given the demands in the marketplace, there has been a shift in strategic focus of RNAi innovators from RNAi triggers to delivery. Silence Therapeutics for example, once competing with Alnylam for RNAi trigger customers, has repositioned itself as an RNAi delivery company, despite controlling some interesting RNAi trigger IP claiming blunt-ended dsRNAs and thermodynamic design rules. Alnylam, as indicated before, also realized the strategic value of delivery and aggressively moved to take control over the industry's most advanced delivery platform, SNALP.

This strategic reorientation is vindicated by the deal activities since 2008 (**Table 4**). More than half of the most significant deals contain delivery as its major component. Product licensing deals take second place and, only then, RNAi triggers third place. Delivery lends itself to business development, because a small company cannot exploit all the therapeutic opportunities that a delivery solution for a given cell/tissue type would offer. Due to the numerous delivery offerings, including those from various non-RNAi companies hoping to capitalize on the delivery demand in RNAi, and the historically high failure rate of early-stage delivery technologies, only the fate of the companies with the most advanced delivery technologies, first and foremost SNALP (Tekmira) and AtuPLEX (Silence Therapeutics), but potentially also sd-rxRNAs (RXi Pharmaceuticals) and Dynamic PolyConjugates (Arrowhead), may be in their own hands as it is clinical validation that most Big Pharma want to see before making any new significant investments. It is therefore critical for these companies to focus their resources on these proof-of-concepts, while the rest will have to keep advancing their technologies with high-quality research and hope that a new wave of RNAi enthusiasm will also lift their respective boats.

Diversification to cast a wider net for partnering. Instead of focusing on reaching clinical or late-preclinical validation events, Marina Biotech has sought to escape the RNAi maelstrom by diversifying its offerings away from RNAi therapeutics to become an oligonucleotide therapeutics one-stop-shop. By this, it wants to take advantage of the quite healthy business activity around some of the non-RNAi oligonucleotide technologies, especially microRNA therapeutics and antisense, and the fact that Big Pharma these days often views RNAi as one of a few RNA Therapeutics alternatives to go after the undruggable targets. Pfizer and Merck for example have housed their RNAi therapeutics activities in "RNA therapeutics" units. The strategy of Marina may have been motivated by a failure to bring its RNAi platform technologies closer to the clinic. Regardless, it was certainly a bold move financially as it kept costs high at a time that capital in RNAi therapeutics quickly dried up. As a result, shareholders witnessed a ~99% drop in the share price since 2008. Moreover, with so many technologies, yet relatively small workforce, such a strategy risks losing scientific depth and ultimately credibility.

Similar things can be said of the merger between Intradigm and Silence Therapeutics in early 2009, although in this case the one-stop-shop idea was pursued still within RNAi therapeutics. The combined company, however, soon gave up on the concept and instead channeled resources into delivery and the development of its lead clinical candidate, Atu027. RXi Pharmaceuticals meanwhile is a more complex case. On the one hand, RXi, once a diversified RNAi therapeutics company, conducted a strategic review and subsequently focused its RNAi activities on self-delivering rxRNAs and on entering a candidate based on the technology (RXI-109) into clinical development, thereby establishing itself as a leader in local/localized delivery. The company, however, finally decided to exit RNAi therapeutics altogether by spinning off the related assets in order to jump onto the therapeutic cancer vaccine bandwagon.

In general, in a capital-constraint environment where partnerships are increasingly geared towards the achievement of technical milestones, and with investors and potential collaborators expecting clinically relevant validation, diversification does not appear to be the right strategy for small pure-play companies. After all, it took Tekmira 500 person-years and over US$200M to turn a single technology, SNALP, into the prolific drug development engine it is today.

Product versus platform focus. Also outside of RNAi therapeutics, it is difficult these days to be a platform company with a relatively early-stage technology as this demands a good part of the investments to go into basic platform development work. Drug companies, however, are largely valued according to their late-stage clinical pipeline with earlier-stage activities, especially preclinical research often commanding no to even negative values. Expeditiously advancing the most developed candidates has therefore become important in its own right, not just for the purpose of validating their underlying technologies.

Alnylam and Quark Pharma are the companies with the most intense product focus. Alnylam in early 2011 launched the 5x15TM program that foresees the company to have five high-impact orphan drug candidates in late-stage clinical development by 2015. This was meant to help biotech investors rationalize a stock market capitalization of $500–600M (and $400M in cash) at the time which was difficult to support based on platform potential alone. In Quark's case, two late and early phase II programs each, and one in phase I meant that it had little choice but spend its capital on its clinical product candidates.

Virtual RNAi therapeutics development. Benitec and Arrowhead Research responded to the RNAi therapeutics capital contraction by adopting virtual drug development models. This model has gained in popularity in the pharmaceutical industry and attempts to increase capital efficiency by outsourcing R&D activities to outside vendors to reduce fixed costs, avoid underutilization of assets, and maximize financial flexibility.

This model may work well when the goal is to develop one-off clinical-stage compounds. It is doubtful, however, that it is an appropriate model for platform technology companies that

Table 4 RNAi therapeutics deals 2008-present

Year (month)	*Focus of deal*	*RNAi asset provider*	*RNAi asset customer*	*Description of agreement*	*Financials*
2008 (March)	Delivery	Silence Therapeutics	AstraZeneca	Delivery collaboration focused on AtuPLEX platform	None disclosed; followed a RNAi trigger deal in 2007
2008 (May)	RNAi triggers	Alnylam	Takeda	Takeda with non-exclusive access to Alnylam's RNAi trigger technology in two therapeutics areas (oncology and metabolic disease); Takeda with first right of refusal for Asian co-development, Alnylam with opt-in into four of Takeda's programs	$100M cash upfront for therapeutic areas, and $50M for transfer of technology (including delivery); per product, up to $171M in development and commercial milestones, plus "significant" royalties on product sales
2008 (June)	Select product candidate	Alnylam	Kyowa Hakko	Kyowa Hakko obtains exclusive Japanese and select Asian rights to RSV drug candidate ALN-RSV01 (in phase II)	$15M cash upfront; up to $78M in development and commercialization milestones, double-digit royalties on sales
2008 (July)	Delivery	Mirus Bio	Roche	Roche buys RNAi delivery company Mirus Bio	$125M in cash
2009 (January)	Select product candidate	Alnylam	Cubist	ALN-RSV01 product co-development (phase II)	$20M cash upfront, up to $82.5M in development and sales milestones, 50:50 profit split in North America, double-digit royalties on net sales outside N.A. and Asia
2009 (February)	RNAi triggers	mdRNA (now: Marina Biotech)	Roche	Roche with non-exclusive license to mdRNA's RNAi trigger technology (meroduplex, Dicer-substrates, UNA-modified siRNAs)	$5M cash upfront; limited royalties
2009 (March)	Delivery	mdRNA (now: Marina Biotech)	Novartis	Novarits with non-exclusive license to IP and know-how regarding mdRNA's DiLa2 liposomal delivery technology	$7.25M in cash
2009 (August)	Delivery and RNAi triggers	Silence Therapeutics	Dainippon Sumitomo	Use of silence delivery technology to demonstrate functional targeting *in vivo*, initially for two targets; expanded to two more in March 2010	$2M cash upfront; milestone from potential option's exercise by end of 2011 (go/no-go)
2010 (January)	Delivery and RNAi triggers	Dicerna	Kyowa Hakko	Delivery collaboration for cancer and endocrinology with Dicerna contributing lipid-based and aptamer delivery, Kyowa liposomes and antibody-targeted delivery; Kyowa Hakko with option to pick up to 10 targets under Dicerna RNAi trigger IP	$4M for first target (in cancer); up to $120M in research funding, development, and commercialization for first target, similar financials for other targets; Dicerna with opt-in for first target
2010 (May)	Delivery	Tekmira	Bristol-Myers Squibbs	Tekmira to provide BMS with SNALP formulations for target validation work at BMS; companies with options to use resulting data for therapeutic development	$3M upfront for predetermined number of SNALP batches
2010 (July)	Select product candidate	Tekmira	US Department of Defense	US DoD to sponsor development of Ebola biodefense agent; preclinical stage program	Up to $34M in cost plus over 3 years through to phase I studies; up to $140 through to licensure
2010 (August)	Delivery	Novosom	Marina Biotech	Marina with exclusive license to Novosom's SMARTICLES liposomal delivery	$3.8M in Marina stock
2010 (August)	Select product candidate	Quark Pharma	Novartis	Novartis with option to exclusively license phase I/II kidney disease drug candidate QPI-1002	$10M for the option; option exercise would trigger option exercise fee with potential to earn >500M of milestones in addition to royalties on product sales
2011 (February)	Select product candidate	Marina Biotech	Debiopharm	Debiopharm with exclusive license to Marina's preclinical bladder cancer candidate	Up to $34M in cost plus over 3 years through to phase I studies; up to $140 through to licensure
2011 (April)	Delivery	Samyang	Takeda	Takeda and Samyang to develop Samyang's delivery technology	Undisclosed financials, including upfront
2011 (September, October)	Delivery	Silence Therapeutics	InteRNA, "Top 10 Pharma", Mirna Therapeutics	Series of early-stage delivery collaborations involving Silence Therapeutics' lipid-based delivery technology	Undisclosed financials
2011 (October)	Delivery and RNAi triggers	Roche	Arrowhead Research	Arrowhead acquires Roche's RNAi assets, including Dynamic PolyConjugate delivery, RNAi trigger rights under Alnylam IP, and three development candidates	$7–9M largely in Arrowhead equity based on Arrowhead stock price on day deal announced; for limited candidates, Roche with right of first negotiation, milestone payments and low single-digit royalties on product sales

Abbreviations: N.A. North America; IP, intellectual property; RNAi, RNA interference; RSV, respiratory syncytial virus; SNALP, stable nucleic acid lipid particles; siRNA, small interfering RNA; UNA, unlocked nucleic acid.

rely on scientific leadership to attract non-dilutive revenues from partnerships and licensing. In RNAi therapeutics, essentially all deals these days (**Table 4**), except for the product-specific ones, include a collaborative research component, illustrating the value pharmaceutical companies attach to the technical expertise of the platform company to ensure that the licensed IP is put to good use. Perhaps realizing that the inadequacy of the virtual model may have accounted for their failure to monetize its RONDEL delivery technology, Arrowhead, with the acquisition of Roche's RNAi assets including a 40 plus research staff in Wisconsin, has started to reinvest in research. The timing, however, is also a gamble that animal spirits are about to return to RNAi therapeutics.

Pure-play survival guidelines. The equity destruction in Marina Biotech shows that pure-play RNAi therapeutics companies can only survive, *i.e.,* be investable, if they can generate non-dilutive revenues. The licensing of platform technologies and product candidates obviously represent the two main sources of such revenues. Other opportunities, however, such as Tekmira's Ebola biodefense contract with the United States government also exist. Between US$70–100M of such non-dilutive revenues was earned over the last 3 years (**Table 4**, plus modest revenues from various unlisted and existing collaborations). This compares to ~US$1B for the same period before that.

Whether these numbers can return to healthier levels depends largely on the results from the ongoing clinical studies with ALN-TTR01, ALN-PCS02, and Atu027. The sector can ill afford negative or inconclusive results because a continuation of the current drought would risk creating a large innovation gap, ultimately to the detriment of everybody involved, small and big. In this period of transition, financial arrangements such as by Benitec with La Jolla Cove Investors, Marina Biotech with Lincoln Park Capital Fund, and Arrowhead Research, also with Lincoln Park Capital Fund, can provide pure-play companies with funding security, yet the flexibility to terminate these dilutive arrangements once better sources of capital present themselves.

Some of the funding shortfall may be compensated for by investments from pharmaceutical companies from Japan and the emerged economies surrounding it (China, Korea, Singapore). The shift of innovative drug development to the East will not stop at RNAi therapeutics, and although Roche's decision has also given investors there some pause, being early-stage and innovation-driven, RNAi therapeutics is still an attractive technology by which these societies can further move up the economic value chain, also in anticipation of the increasing number of citizens that will have access to such medicines. First-generation RNAi therapeutics innovator companies from the West can capitalize on this demand by monetizing their RNAi assets for markets that, for geographic and cultural reasons, are of less strategic interest to them.

The Big Pharma perspective. Despite its $2.5–3B invested in RNAi therapeutics in 2005–08, Big Pharma has yet to bring a single such compound into clinical development. It is thus no surprise that RNAi therapeutics has become a bad career strategy in Big Pharma, and it explains why the bar for new investments has increased considerably. Roche, Pfizer, and Abbott Labs have terminated in-house RNAi therapeutics development altogether, others like Merck and AstraZeneca have reduced their activities.

There are a number of explanations for this track record und unhappiness. In retrospect, the RNAi trigger IP licenses which have since lost much of their strategic value account for approximately half of the waste. Big Pharma may also have relied too much on assurances by pure-play companies that delivery technologies were more mature than they really were. It is interesting for example that Roche's Factor VII patent application (WO 2010/055041) features Alnylam's "lipidoid" technology for the rodent studies, but then switched to Tekmira's SNALP liposomes for the nonhuman primate part of the patent application. Major contributors to waste were also platform development strategies that may work for small molecules, but go against the scientific grain of RNAi therapeutics. This includes selecting indications based on sales predictions and therapeutic franchises rather than based on in which cell/tissue type knockdown can be technically achieved; similarly failing to follow the science in pursuing delivery based on patient convenience; and finally putting the cart before the horse by first focusing on developing clinical pharmacology assays and optimizing manufacturing[33] instead of on overcoming the actual rate-limiting challenges. This paradox is symbolized by AstraZeneca's 2011 partnership with PTC therapeutics in RNA-targeted therapeutics, which aims at modulating RNA processing for anticancer therapy using orally available small molecules, not oligonucleotides. To some extent Big Pharma needs to trust that following the science maximizes the chance of developing the innovative, high-impact medicines for diseases of high unmet medical need which have become the profit centers of the industry and which RNAi therapeutics, as a genetic medicine, is ideally positioned to address.

Despite these failures, most Big Pharma companies either still pursue RNAi therapeutics or at least follow it closely, understanding that it is more a question of when and not of whether RNAi therapeutics will become a major new drug development engine or not. The causes of their failure immediately suggest how RNAi asset buyers in general, not only Big Pharma, can improve their RNAi therapeutics odds. Fundamentally, it needs to be questioned whether Big Pharma is the right place for RNAi innovation. While the acquisitions of established RNAi therapeutics research groups allowed Merck and Roche to be the source of at least some innovation, efforts to grow RNAi therapeutics platform capabilities from the ground up internally (e.g., Abbott, GSK, Novartis) or after acquiring non-RNAi oligonucleotide technologies (e.g., Pfizer) have been less successful. In some cases, internal groups may also have the damaging effect of posing an obstacle to taking (more capital-efficient) advantage of superior outside innovation in favor of home-brew versions of the same technologies (e.g., liposomal delivery).

When shopping for RNAi technologies, it is the responsibility of buyers to deeply familiarize themselves with the field to spot the few good technologies in a sea of questionable offerings. Purchase decisions should also not be primarily motivated by what their peers are doing. As the 2005–08 bubble illustrates, such herd instinct can lead to costly mistakes, and in this part of the business cycle may mean the failure to take advantage of the severely depressed asset prices. In fact,

from a financial risk-reward perspective, this may be the best time ever to become involved in RNAi therapeutics development. This also applies to pharmaceutical companies and economic policy makers in the emerged economies which can transfer the most promising technologies for a fraction of what it cost to develop them.

BUSINESS OUTLOOK

As noted before, the results from the ongoing ALN-TTR01 and ALN-PCS02 SNALP-based clinical studies will have a major impact on the RNAi therapeutics business climate for at least the next 2 years. Data from the AtuPLEX-based Atu027 trial has the potential to amplify the SNALP-driven return in bullishness, but because the AtuPLEX-based pipeline is still thin, is unlikely to carry a sentiment shift by itself. This also applies to any unexpected positive data from Quark/Pfizer's phase II study in wet age-related macular edema (patient recruitment completed), as like the rest of Quark's pipeline, this candidate does not have platform character.

With capital spread thin in the industry, negative results could have devastating consequences for companies in need of financing. On the other hand, operational costs have been reduced already and valuations fallen so deep, that should the nascent recovery that set in with the ALN-VSP02 and Atu027 data presentations at ASCO 2011 find confirmation later this year (2011), being invested now could be quite profitable. Despite the more linear advance of the science, the business of RNAi therapeutics is thus likely to remain a cyclical one.

The shift in Big Pharma's involvement in RNAi therapeutics from in-house platform development to product-specific licensing and co-development is likely to persist, also because of the structural changes in the industry towards the outsourcing of research. Their place may be taken by medium-sized pharmaceutical companies and new players from the emerged economies, governments, and companies, which view RNAi therapeutics as a potentially disruptive technology where they still have the chance to become leaders and thereby establish themselves in innovative drug development.

Business in ddRNAi therapeutics is somewhat uncoupled from RNAi therapeutics triggered by synthetic RNAi triggers, mainly due to the technical differences which make it more similar to traditional gene therapy. It is, however, set to gain traction, not just because of numerous supporting preclinical data,[15,24,25] but also because of it being part of the gene therapy field which is experiencing a revival[47] following a boom and bust similar to what RNAi therapeutics has just gone through. But whatever the latest trends in the pharmaceutical industry, healthcare systems, and global economy, the best advice to all participants in RNAi therapeutics is to operate on the assumption that in 5–10 years, when first RNAi therapeutics should be commercialized, innovative drugs that help the lives of seriously ill people will more likely than not make a profit.

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