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THE STATE OF RNA INTERFERENCE

DRUG REVIEW PROFILE

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PIPELINE SPOTLIGHT

- **Five late-stage products in Lilly's pipeline could launch by end of decade**, exec says at UBS Global Life Sciences Conference. Mid- and late-stage pipeline opportunities, including gamma secretase inhibitor for Alzheimer's and long-acting versions of ***Byetta*** and ***Zyprexa***, fuel Lilly's optimism **10**

- **Pfizer is retooling its infectious disease portfolio to focus on specialty diseases,** particularly HIV and hepatitis C. Execs outlined the pipeline during the Interscience Conference on Antimicrobial Agents and Chemotherapy meeting. Areas of R&D focus, including next-generation CCR5 receptor antagonists and non-nucleoside reverse transcriptase inhibitors, are competitive, however. Pfizer is also proceeding with development of a polymerase inhibitor for HCV despite side effects seen with other investigational drugs in the class..... **8**

- **Sanofi-Aventis expanding rimonabant diabetes program; firm is undertaking multiple studies** to support ***Zimulti*** filing for type 2 diabetes, expected in 2009. One study will look at the cannabinoid-1 receptor antagonist as monotherapy, while the rest evaluate combination use with metformin or other existing therapies. The RESONATE trial, slated to begin in the fourth quarter of 2008, will evaluate rimonabant plus metformin versus Merck's dipeptidyl peptidase-4 inhibitor ***Januvia*** (sitagliptin). Sanofi's other novel diabetes therapies also highlighted at R&D presentation **11**

- **Sanofi-Aventis looks to establish *Lovenox* follow-on AVE5026 through head-to-head trials** showing the ultra low weight heparin as more effective than enoxaparin in reducing venous thromboembolic events, firm says. Company unveiled Phase II data on AVE5026 during Sept. 17 R&D presentation. Phase III trials are starting, with the first regulatory filings slated for 2010 and 2011 ..... **13**

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Solvay's tedisamil PDUFA date extended: FDA extends the review clock on Solvay's tedisamil NDA for the treatment of recent onset atrial fibrillation or atrial flutter, setting a new user fee date of Jan. 19, 2008. The company submitted additional clinical pharmacokinetic data, which set the review back for the class III anti-arrhythmic potassium blocker. An FDA Cardio-Renal Drugs Advisory Committee meeting is scheduled for Dec.11-12 to discuss the application....

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The State Of RNA Interference Therapeutics: Delivery Is Everything

With interest – and dealmaking – in RNA interference technology soaring, all eyes are on how to solve the delivery challenges of this new class of therapeutics that backers say has the promise to be as big as monoclonal antibodies.

Discovered in mammals less than a decade ago, RNAi is a natural process in cells that blocks messenger RNA from synthesizing proteins and thus silencing the genes that cause many diseases. Heralded as the next holy grail of drug development, the new gene-silencing technology – which was granted the Nobel Prize in Medicine in 2006 – is being looked to as the source of potential cures for genetic disorders such as Parkinson's and viruses like hepatitis C and HIV, as well as numerous cancers (*see chart below on history of RNAi)*.

Over the past year the RNAi field has taken off, transitioning from a few companies that were created around the basic science to a competitive group of biotechs to partnerships with big pharma companies looking to invest in the nascent technology *(see sidebar on RNAi business development, p. 7)*.

But now that companies have embraced RNAi technology and are funding development, delivery of the technology remains the largest hurdle to clear because RNAi involves macromolecules that are simply too big to be uptaken by most cells.

Macromolecule delivery can be direct or systemic. Direct delivery involves inserting the therapeutic directly into the target organ, such as the eye via injection for treatment of macular degeneration or via inhaler for lung disorders.

"We have numerous instances of direct RNAi delivery where we can administer the drug to the compartment that's important and see uptake of the drug and down regulation of the target that we're concerned with – we see that in the brain, the eye, the lung and there are other compartments," Alnylam VP-Clinical Research Akshay Vaishnaw said in an interview with *Pharmaceutical Approvals Monthly*.

Companies developing these types of delivery therapeutics are the furthest in the pipeline and could be first out of the gate.

A Brief History of RNAi

1992: RNAi mechanism identified in plants.
1993: Dharmacon formed to develop technology for RNA oligonucleotide synthesis. When RNAi emerged in the late 1990s, Dharmacon turned to siRNA research tools.
1997: Andrew Fire (Carnegie Institute), working with Craig Mello (U Mass), discovers that RNAi is present in animals. Since the central dogma of molecular biology is that DNA is transcribed into RNA, and then RNA is translated into a protein, they knew that there was gene suppression going on and that it was post transcriptional, which means it was the RNA that was being degraded.
2001: Thomas Tuschl at Germany's Max Planck Institute published in April 2001 issue of Nature on isolating fragment of RNA called small interfering RNAs, or siRNAs, that could inhibit genes without broad killing effect seen earlier.
2002: Anton McCaffrey and Mark Kay at Stanford University announced RNAi treatment controlled hepatitis C in mice – first time RNAi technology conducted in animals using viral vectors.
2002: Phillip Sharp and colleagues at MIT announced they could interrupt the HIV virus in vitro but not yet in humans. Sharp co-founds Alnylam with Thomas Tuschl. The company holds patents to discoveries by Tuschl and Sharp.
2003: Virologist Sara Hall and Mark Kay form Avocel and announce compound for HCV that targets multiple targets using AAV vector for systemic delivery.
2004: Acuity (now Opko) initiates first RNAi clinical trial for treatment of macular degeneration. Clinical results indicate that after two months, 25 percent of patients had significantly clearer vision. Product expected to hit the market in 2009.
2006: John Rossi, City of Hope, engineers RNAi therapy that targets multiple HIV genes; he extracts stem cells from bone marrow to genetically alter the cells with RNAi therapy and then transfers them back to the patient.
2006: Merck acquires Sirna, one of the first companies to bring RNAi therapy into clinical trials with Sirna027.
2007: Deals multiply as more RNAi candidates enter the clinical pipeline and solutions begin to emerge for systemic delivery of RNAi therapies.

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Direct delivery products such as Opko Health's bevasiranib for the treatment of wet age-related macular degeneration is positioned to be the first RNAi therapeutic on the market – it was the first RNAi drug to reach Phase III trials. Opko was formed in March when originator Acuity Pharmaceuticals joined forces with Froptix and eXegenics.

Bevasiranib is a small interfering RNA (siRNA) that silences the genes that produce vascular endothelial growth factor. The treatment is injected directly into the eye every eight or 12 weeks. Dosing in the Phase III COBALT (Combining Bevasiranib and Lucentis Therapy) trial began Aug. 30, Opko reports.

Device maker Medtronic and RNAi pioneer Alnylam are developing a combination product to treat Huntington's Disease that delivers an RNAi therapeutic directly to the brain via an implantable infusion pump. The companies are also considering a similar combination product to treat other central nervous system disorders, such as Parkinson's disease.

Alnylam's lead candidate ALN-RSV01, now in Phase II, is being developed for the treatment of respiratory syncytial virus. The compound is delivered directly to the lungs via inhaler to silence the nucleocapside protein in infected lung cells, which neutralizes and prevents the spread of the virus.

The trial uses an experimental infection model in which healthy adults are infected with a respiratory virus in a carefully controlled environment to evaluate RSV01 in that setting before moving ahead to authentic settings.

Systemic Delivery Next Hurdle To Clear

While options for direct delivery of RNAi therapeutics abound and likely will be the first wave of the drugs to make it through development, coming up with more attractive systemic delivery options will be trickier.

For systemic delivery, the RNAi must be altered to penetrate cells. There are two basic approaches for systemic delivery. One option is to chemically alter siRNA or package it with other molecules to allow entry. The other option is to encapsulate RNAi into a viral vector to express, or drag, it across the cell membrane.

The molecular mediator that allows the degradation of messenger RNA to occur is siRNA, which is covered under the Tuschl 2 patent and is Alnylam's "crown jewel," Vaishnaw said. Alnylam contends that it owns the gate that companies will need to walk through to gain entry in the RNAi space.

Founded by scientists Phillip Sharp and Thomas Tuschl, Alnylam holds the largest intellectual property estate in the RNAi space (*see sidebar on RNAi IP*).

"If siRNAs are ever going to be drugs that get developed and approved, then the constraints around them are well known: they have to be a certain size (21-23 nucleotides in length), they have to be double-stranded in nature and they generally work best when they are in a certain staggered duplex," Vaishnaw explained. "That's what the natural pathway uses and that's how we design our drugs."

Companies will also need the IP that says they can use RNAi therapeutics to silence a target in a mammalian cell, which Alnylam holds, Vaishnaw stressed.

The 800-Pound Gorilla

"We are the 800-Pound gorilla both in terms of the IP as well as the progress that's been made since the inception of the company five years ago," Vaishnaw said. "We've taken molecules from cells to animals

RNAi Intellectual Property

With a few key patents covering the basic science of RNA interference, intellectual property is a critical issue for drug development. Here are the core RNAi patents (and their owners) issued in the United States:

1. Fire and Mello patent (Carnegie Institute) – covers siRNAs in vitro. All entries in RNAi field must do a blanket nonexclusive license for an upfront $85,000 fee.
2. Graham patent (Mick Graham) – covers broad claims for all in vivo and in vitro use of expressed RNAi.
3. Tuschl 1 (UMass Medical School, MIT, Whitehead Institute and Max Planck Society) – covers inhibition of target genes with double-stranded RNA 21-23 nucleotides in length.
4. Tuschl 2 (Max Planck, MIT and Mass Med School) – covers small interfering RNA, or siRNAs, for silencing genes in mammals. When Alnylam was founded, MIT granted Alnylam exclusive license to the Tuschl 2 estate, which included methods and manufacturing.
5. Crooke patents (Isis, licensed to Alnylam) – covers degradation of target mRNA mediated by chemically modified RNAi-like oligonucleotides.
6. Sirna patent for short interfering RNA (now owned by Merck).

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to man, and [now] we're on the verge of an astonishing proof of concept by the end of the year. And we've also tackled one of the most important questions, which is how does one effectively deliver these therapeutics?"

For systemic delivery, Alnylam's liposomal approach of encapsulating a drug in liposomes and injecting it intravenously shows great promise, he said. Other approaches include antibody conjugation or peptide conjugation.

The company published a study in the Sept. 17 issue of Nature in which lipid conjugates of siRNAs that facilitate in vivo systemic delivery were found to associate with circulating lipoprotein particles and to achieve cellular uptake through receptors for low-density lipoprotein and high-density lipoproteins. Results of that study have implications for the company's hypercholesterolemia RNAi therapeutic, which is directed to a disease target called PCSK9.

Targeting Multiple Cancer Pathways

The other systemic target Alnylam is chasing is liver cancer. ALNVSP01 encapsulates two siRNAs in one liposomal formulation that targets two different cancer pathways: VEGF and kinase spindle protein. "So we think that anti-angiogenic and the antiproliferative approach is a powerful way to go at a pathology. … You can't ideally tackle most cancers by just one drug targeting one pathway. So this combined approach, which RNAi affords, allows you to go at multiple intervention points in a cancer," Vaishnaw said.

Both PCSK9 and VSP01 are IND candidates for 2007, according to Vaishnaw.

Alnylam has recently partnered with Isis to form a new company, Regulus, dedicated to microRNA antagonists. The two companies cross-licensed each other's IP for RNAi. Isis specializes in oligonucleotide therapies using antisense or single-stranded approaches for systemic delivery.

Hitting Multiple HCV Pathway Targets

Tacere Therapeutics, which is focusing on infectious diseases using RNAi, is using the vector approach to systemic delivery.

Tacere's lead RNAi compound is triple vector TT-033, which is composed of three individual short hairpin RNAs targeting three independent regions of hepatitis C simultaneously. HCV, like HIV, is an RNA virus that mutates very quickly, so "you have to hit multiple regions simultaneously," Tacere Therapeutics CEO Sara Hall told *Pharmaceutical Approvals Monthly.*

"If you're using something like RNA interference where you're targeting the viral sequences themselves, and if you're only targeting one 19-23 nucleotide region of a fairly long viral genome, it can introduce a silent point mutation that doesn't even affect the fitness of the virus, but you completely lose the inhibitory activity of the RNAi drug," she said. "We knew from our experience of RNA viruses that we had to hit multiple regions simultaneously."

"By using the ability of expressed RNAi, we could string multiple sequences together. So not only could we multitarget them, but we could also cross genotypes of HCV," Hall said. There are six predominant genotypes of HCV worldwide. "We looked at patient isolates across all the different genotypes and pulled out conserved regions, so that between the three targets we could hit basically every genotype of HCV. Because the capability was there, we just captured the full power of RNAi."

Delivering RNAi to the liver is difficult because it is a heterogenous organ with many different cell types that are difficult to penetrate. Tacere chose an adeno-associated virus – a very small virus, which is nonpathogenic and replication incompetent. A protein capsid, the vector is gutted so that it has no viral genes in it but contains the three shRNAs.

"FDA likes the AAV because it doesn't cause a primary immune response and there is no targeted integration of it like retroviruses … your body will clear it over time," Hall explains. "RNAi is an incredibly powerful mechanism because it is totally catalytic and doesn't require much input. … If you can knock down the viral load two logs or greater for 12 weeks, that's indicative of a sustained biologic response and that's the approval criteria you need to have," she said, adding that HCV does not integrate, and since there is no replenishing source, once it is cleaved, the virus is gone.

Tacere had a pre-IND meeting with FDA in June and got "a very big thumbs up from CBER," Hall said. "They're really excited about it because this is only the third RNAi drug that they've seen on the scene" (*see chart of compounds in the pipeline, p.* 6). She explained that the two frontrunners for AMD indications (both direct delivery) went through FDA's Center for Drugs. Tacere anticipates initiating Phase I trials in the second or third quarter of 2008, and is in the process of finalizing protocols with FDA.

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RNAi Pipeline Candidates

Selected compounds in the RNAi pipeline; list may not include all candidates.

Company & compound	Indication/target	Phase	Delivery method
Opko (formerly Acuity) Bevasiranib	AMD (targets VEGF)	III	Direct eye injection
Alnylam ALN-RSV01	RSV	II	Direct to lungs via inhaler
Alnylam [unnamed]	Hypercholesterolemia (targets PCSK9)	IND 2007 candidate	Systemic (blood) liposomal conjugation
Alnylam ALN-VSP01	Liver cancer (targets VEGF and KSP)	IND 2007 candidate	Systemic (liver) liposomal conjugation
Allergan AGN211745 (previously Sirna 027)	Wet AMD	II	Direct eye injection
City of Hope [unnamed]	HIV AIDS	I	Systemic – lentiviral vector
Silence Therapeutics RIP801i	AMD	I	Direct eye injection
Tacere TT-033	Hepatitis C	IND 2008 candidate	Systemic – AAV vector
Nucleonics NUCB1000	Hepatitis B	IND candidate	Systemic – expressed plasmid in a liposome

Tacere and Japanese Oncolys BioPharma entered into a strategic development alliance whereby Oncolys acquires the Asian rights of TT-033, which the company will develop as OBP-701.

City of Hope HIV RNAi Stem-Cell Therapy

Meanwhile, City of Hope, a Los Angeles-based research hospital, has begun Phase I trials of its RNAi therapy using a lentiviral vector to encapsulate three different genetically engineered genes into stem cells to fight the HIV virus.

"In essence, what we did was make this siRNA inside of cells but without any virus being present, so there's no target," Division of Molecular Biology Professor John Rossi said. "Previous studies had demonstrated that certain combinations of siRNAs activate the cell's innate immune response. Since we had one of these combinations in our siRNA targeting HIV, it became paramount to determine whether or not this combination was active when it was produced by the cell. Our focus was to identify whether there was any toxic side effect from our process. And there wasn't."

The Phase I trial will study the RNAi therapeutic in five patients who have both AIDS and AIDS-related lymphoma.

Customized Lentiviral Vectors To The Rescue

Lentigen custom-designs lentiviral vectors for companies competing in the RNAi space. It recently joined forces with Dharmacon, a company that assists with RNAi discovery and technology, to launch a RNAi research product called SmartVector that delivers highly specific RNA constructs with better delivery technologies.

The SmartVector "incorporates the proprietary microRNA and RNAi algorithms that Dharmacon has spent a lot of time developing," Lentigen CEO Boro Dropulic told *Pharmaceutical Approvals Monthly*. Dharmacon focused on siRNAs, but they also tend to have a short-term effect and some cell types are more difficult to penetrate, Dropulic said.

"Lentiviral vectors solve both of those two fundamental problems. You can get stable expression of the RNAi in the cell so that you can create cell lines with knockdowns, and lentiviral vectors allow you to get RNAi into difficult-to-transfuse cells," he said.

Dharmacon's RNAi is imbedded with a microRNA transcript, which allows for better processing because the RNAi functions best when it is cut

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down into its minimal pieces within the cell, he explained.

One of the big hurdles in RNAi research is that an RNAi is developed against a sequence, but it not only knockdowns that sequence, it can also knockdown another sequence, giving a nonspecific effect, Dropulic said. "And so the algorithms that Dharmacon has developed that are now incorporated into our lentiviral backbone solve a lot of these problems in that you get very high specificity and low off-target effects."

– *Tamra Sami* (t.sami@elsevier.com)

The Business Of RNAi: Some Of The Deals Behind The Boom

The soaring interest in RNA interference is reflected in the ever-increasing deals – which have heated up as the RNAi field has attracted the attention of big pharma – and new companies being created in that space.

Merck was among the first big firms to sign on to RNAi, with the acquisition of Sirna Therapeutics in October 2006 in a deal worth approximately $1.1 billion. Sirna had accumulated numerous patents for RNAi and was developing an RNAi therapeutic, which is now being developed by Allergan for macular degeneration. Merck also has a partnership with Artemis Pharmaceuticals (a subsidiary of Exelexis) to construct short interference RNA mouse studies.

AstraZeneca and Roche followed with similar deals with Silence Therapeutics and Alnylam, respectively. Pfizer has also made forays into the RNAi field, with a licensing agreement with Sigma-Aldrich for its DNA-directed RNAi technology, signed in January 2007, and an earlier license for Quark Biotech's RTP-801 gene.

Not surprisingly, given its leadership in the field and its IP portfolio, Alnylam is at the center of many of the deals in the RNAi space. One of its first major deals was a collaboration with Novartis to jointly advance RNAi therapeutics for pandemic flu, announced in February 2006. In September 2006, Alnylam and Biogen Idec announced a collaboration to develop RNAi therapeutics for the potential treatment of progressive multifocal leukoencephalopathy. In July, Alnylam expanded its existing partnership with device manufacturer Medtronic to include development of an RNAi therapeutic for Huntington's disease.

Alnylam and Roche inked a deal in July that gives Roche a nonexclusive license to Alnylam's technology platform for developing RNAi therapeutics. The alliance, which includes $331 million in upfront cash payments and equity investment, will initially cover four therapeutic areas: oncology, respiratory diseases, metabolic diseases and certain liver diseases. Alnylam and Roche also will collaborate on RNAi drug discovery for one or more disease targets in these therapeutic areas.

Alnylam severed its ties with Merck last month to "protect our intellectual property, our know-how and other important confidential information and really distance ourselves from them so they wouldn't have access to our capabilities," Alnylam's Chief Operating Officer Barry Greene said in an interview. The move was not entirely unexpected, due to Merck's acquisition of Sirna. Merck acquired a company "that had chosen to oppose certain European patents of ours, following the European patent opposition process, and … quite frankly, that's not someone we wanted to collaborate with," Greene said.

Alnylam has recently partnered with Isis to form a new company, Regulus, dedicated to microRNA antagonists. The two companies cross-licensed each other's IP for RNAi. Isis specializes in oligonucleotide therapies using antisense or single-stranded approaches for systemic delivery.

Regulus is representative of another trend in the RNAi space: partnerships and mergers among small biotechs looking to leverage their IP and carve out specialties in specific areas of RNAi technology. In March 2006, Acuity, Froptix and eXegenuics joined together to form a company called Opko Health, which will advance Acuity's RNAi therapeutic bevasiranib for treatment of wet age-related macular degeneration. Other RNAi players include Tacere, Nastech, and CytRx, which has spun off its RNAi division as RXi Pharmaceuticals.

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