

Novartis exit caps tough period for RNAi research



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Biotech market performance has been woeful over the past two months, but perhaps no cluster of companies has exemplified this collapse quite like the developers of RNA interference (RNAi) therapies. News this week that the pharma giant Novartis has mostly withdrawn from the space, citing delivery and target issues, will not lift confidence that this science will spawn a blockbuster anytime soon.

Alnylam is desperately close to proving that RNAi can change the course of a genetically inherited disease, and has got the endorsement of Sanofi along the way. Yet aside from its work in amyloidosis, progress in RNAi has been slow and appears to have led to another round of disappointment among investors and big pharma executives alike (see tables).

Carnage

The carnage in biotech has been well documented and has done significant damage to dozens if not hundreds of companies along the way, not the least of them Gilead Sciences and Biogen Idec. However, RNAi companies have suffered worse than the average of the Nasdaq biotechnology index – only Spain’s Grupo Zeltia, which has an RNAi-focused subsidiary called Sylentis, and Australia’s Benitec can boast of a better performance since the Nasdaq biotech index hit its record high February 21.

Small companies' relative frothiness in the midst of the biotech bull market of 2012 and 2013 no doubt had something to do with their collapse. Arrowhead Research in particular had seen its valuation skyrocket, and even with a 48% fall since February 21 it is worth many times more today than it was at the end of 2012 – mostly on the strength of a study in one chimpanzee ([EP Vantage interview – Arrowhead looks to evolve beyond the chimp](#), November 1, 2013).

Public companies (outside big pharma) working in RNAi			
	Market capitalisation (\$m)		
Company (US unless specified)	2012 YE	Current	Decline since Feb 21st
Alnylam Pharmaceuticals	958	3,516	(37%)
Arrowhead Research	29	518	(48%)
Benitec (Australia)	30	130	4%
Bio-Path Holdings	22	245	(35%)
Dicerna Pharmaceuticals	n/a	284	(59%)
Grupo Zeltia (Spain)	364	741	(12%)
Marina Biotech	7	12	(26%)
RXi Pharmaceuticals	12	46	(27%)
Silence Therapeutics (UK)	102	198	(27%)
Tekmira Pharmaceuticals	72	280	(38%)
Nasdaq biotechnology index			(18%)

But it is not just market conditions. Enthusiasm for RNAi has waxed and waned, and the fact that clinical headway has been sluggish cannot be helping. Eight years on from the Nobel Prize in Medicine for Andrew Fire

and Craig Mello for discovering the science, only Alnylam's patisiran is making a serious run at the market in phase III, in the orphan condition familial amyloidotic polyneuropathy caused by transthyretin-mediated amyloidosis.

Sanofi's return to the space in January was taken as a sign that interest had renewed ([*Alnylam lives the biotech dream as big pharma returns to RNAi*](#), January 13, 2014). That has surely been reversed with Novartis' departure.

The Swiss group blamed "ongoing challenges with formulation and delivery and the reality that the current range of medically relevant targets where siRNA may be used is quite narrow". A small group will remain working in the field and look for partnering opportunities, but most of the 26 full-time staff in RNAi will be reassigned or let go.

In 2001 Novartis had selected 31 disease targets from Alnylam's research portfolio as part of a collaboration signed in 2005. The fate of these projects is not clear.

Big pharma goes, who remains?

Where does development stand? Since Merck & Co has also exited the field this year by selling off Sirna Therapeutics to Alnylam for pennies on the dollar, big pharma has largely exited this field with the exception of Sanofi; what remains are a handful of publicly traded small-cap companies, and only Alnylam has an active trial in phase III.

Ongoing trials testing RNAi-based therapeutics

Status	Project	Company	Conditions	Enrolment	Primary completion date (CT.gov)	NCT ID
Phase III	Patisiran	Alnylam	TTR-mediated amyloidosis	200	01/01/2017	NCT01960348
Phase II	Patisiran	Alnylam	TTR-mediated amyloidosis	28	01/12/2016	NCT01961921
	ALN-TTRsc	Alnylam	TTR-mediated amyloidosis	15	01/10/2014	NCT01981837
	RXI-109	RXi Pharmaceuticals	Hypertrophic scar	32	01/06/2015	NCT02030275
	ARC-520	Arrowhead Research	Hepatitis B, chronic	16	01/12/2014	NCT02065336
	RXI-109	RXi Pharmaceuticals	Keloid	16	01/12/2014	NCT02079168
Phase I/II	TKM-PLK1	Tekmira	Neuroendocrine tumors and adrenocortical carcinoma	56	01/05/2014	NCT01262235
	SYL1001	Grupo Zeltia (Sylentis unit)	Ocular pain/dry eye syndrome	60	01/07/2013	NCT01776658
	Atu027	Silence Therapeutics	Carcinoma, pancreatic ductal	30	01/08/2015	NCT01808638
	TT-034	Benitec	Hepatitis C	14	01/09/2015	NCT01899092
Phase I	ARC-520	Arrowhead Research	Healthy	48	01/06/2014	NCT01872065
	ALN-AT3	Alnylam	Haemophilia A/haemophilia B	42	01/10/2015	NCT02035605
	TKM-Ebola	Tekmira	Ebola virus infection	28	01/07/2014	NCT02041715
	Patisiran	Alnylam	TTR-mediated amyloidosis	12	01/06/2014	NCT02053454

Other companies have advanced a long way only to report mixed or disappointing data at the proof-of-concept stage. Isarna's trabadersen, for example, showed mostly non-significant improvements over standard chemotherapy in high-grade glioma nearly three years ago, and its phase III work in this area has been abandoned.

Yet activity is still under way in phase II. Alnylam's interest in amyloidosis has prompted two other trials of patisiran as well as a third for ALN-TTRsc, while RXi Pharmaceuticals has two trials of RXI-109 testing it in the similar conditions of hypertrophic scars and keloids, and Arrowhead has advanced its chronic hepatitis B project ARC-520 from chimps into humans. At best, assuming continued clinical success, these are several years from launch.

The problem for the field is that it is asking its partners and investors to remain patient while a so-far unproven – as a human therapeutic, anyway – science tries to prove itself. This might be an acceptable risk for visionaries, but for momentum traders it is a big problem. The market performance of RNAi specialists shows just how big.

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