IN brief

Interest resparks in RNAi

In August, Weston, Massachusetts–based Biogen Idec partnered with Regulus Therapeutics of La Jolla, California, to identify microRNA biomarkers in the blood of multiple sclerosis patients. A few days later, Regulus (a joint venture between Alnylam and Isis Pharmaceuticals) forged a deal with London-based AstraZeneca, and in October the microRNA drug developer launched its initial public offering. The resurgence in RNA interference (RNAi) has touched agbiotech, too. In August, Monsanto of St. Louis, paid RNAi pioneer Alnylam $29.2 million upfront and undisclosed milestones to use the company's gene silencing technology in pest control. In September, the Swiss agbiotech firm, Basel-based Syngenta, agreed to pay $523 (€403) million for Devgen, of Ghent, Belgium, a developer of RNAi technology also directed toward biological pest control. The slew of recent deals confirms that companies have once again become confident that RNA-based technologies will pay off, says Edward Tenthoff, senior research analyst at PiperJaffray in New York. Much of the renewed optimism surrounding RNAi technology has been fuelled by the recent success of Alnylam, says Alan Carr, senior biotech analyst at Needham and Company in New York. For RNA-based therapeutics, delivery into specific body sites remained a challenge and several companies pulled out of the field citing poor prospects for a drug (*Nat. Biotechnol.* **29**, 93–94, 2011). But during the last year, Alnylam located in Cambridge, Massachusetts, has shown that this challenge can be overcome, Carr says. In clinical trials two RNAi drugs—ALN-TTR that targets the transthyretin gene to treat TTR-mediated amyloidosis and ALN-PCS to treat hypercholesterolemia—both showed therapeutic effect. The field experienced a financial drought for a few years, Tenthoff explains. "But the early deals were about technology platforms, not drugs. Now the focus has shifted to drugs. That's reinvigorating this whole field." During the same week that Regulus went public, Sarepta Therapeutics of Cambridge, Massachusetts, announced that their drug eteplirsen stimulated muscle cells to produce dystrophin in boys suffering from a specific mutation causing Duchenne muscular dystrophy (*Nat. Biotechnol.* **30**, 904–905, 2012). Eteplirsen is an antisense technology that modulates alternative splicing of pre-mRNA. On October 18, the US Food and Drug Administration's Endocrinologic and Metabolic Drugs Advisory Committee met to discuss Isis Pharmaceuticals of Carlsbad, California, and partner Sanofi's data for Kynamro (mipomersen), an antisense inhibitor of apoB-100, intended to treat severe familial hypercholesterolemia. If approved, Kynamro will be the first antisense-based drug on the market since Isis launched the now-withdrawn Fomivirsen in 1998 to treat cytomegalovirus retinitis in AIDS patients. *Gunjan Sinha*

Table 1 Selected multiple myeloma drugs in late-stage development

Company/ location	Drug	Compound	Target	Status
PharmaMar	Aplidin	Cyclodepsipeptide derived from the marine tunicate *Aplidium albicans*	VEGF (vascular endothelial growth factor)	Phase 3
Bristol-Myers Squibb	Elotuzumab	Humanized monoclonal antibody	Cell surface glycoprotein CS1 highly expressed on myeloma cells and minimally on normal cells	Phase 3
Novartis	Faridak	Small molecule	Histone deacetylase	Phase 3
AB Science	Masitinib	Small molecule, structural analog of Gleevec (imatinib)	Fibroblast growth factor receptor, KIT/c-KIT, platelet-derived growth factor receptor	Phase 3
Takeda	MLN9708	Small molecule	Proteasome	Phase 3
Aeterna Zentaris	Perifosine	Small molecule	Phosphatidyl inositol 3 phosphate kinase/AKT pathway	Phase 3
Eli Lilly	Tabalumab	Human monoclonal antibody	BLyS/BAFF/TACI/BCMA receptor	Phase 2/3

Source: BioMedTracker. BlyS: B lymphocyte stimulator; BAFF, B-cell activating factor; TACI, transmembrane activator and calcium-modulator and cyclophilin ligand interactor; BCMA, B-cell maturation activator.

One promising antibody target is CD38, a signaling molecule that is highly overexpressed on plasma cells and much less on other kinds of immune cells. In August, Genmab, a Danish biotech based in Copenhagen, struck a $1.1-billion deal with Johnson & Johnson subsidiary Janssen Biotech to commercialize its antibody, daratumumab, currently in phase 1/2 trials. The fully human monoclonal antibody is thought to target CD38, a transmembrane glycoprotein expressed in hematopoietic and nonhematopoietic lineage cells. Daramtumumab kills multiple myeloma cells in several ways, explains Jan G.J. van de Winkel, Genmab's CEO, such as inducing apoptosis, antibody-dependent phagocytosis and antibody-dependent cellular cytotoxicity. Its benign safety profile makes it an attractive possible maintenance therapy, he adds—or even a preventative treatment that could potentially be used in the so-called smoldering stage of the disease, when plasma cells are in a premalignant state. The company hopes to be ready to seek approval for daratumumab in 2015, van de Winkel says. Two other anti-CD38 antibodies—one from Waltham, Massachusetts–based biotech Immunogen and pharmaceutical giant Sanofi, and the other from Martinsried, Germany–based biotech company MorphoSys—are also under development, though they are further behind and may have weaker efficacy.

Bristol-Myers Squibb is testing a different antibody therapy for multiple myeloma, which has already reached phase 3; the trial, launched last year, is exploring the efficacy of a humanized monoclonal called elotuzumab in combination with Revlimid. Elotuzumab is directed against CS1, a cell-surface glycoprotein that is expressed in upwards of 90% of multiple myeloma cells and a few other cell types. The molecule's role in multiple myeloma cells is not well understood, but studies suggest it helps tumor cells adhere to stromal cells in the bone marrow. Elotuzumab has a variety of effects on multiple myeloma cells, but is thought to kill them by antibody-dependent cellular cytotoxicity.

Other candidates, which are just trickling into clinical testing, target a host of different mechanisms of action, such as kinase, heat shock protein 90 and histone deacetylase inhibition. "In some ways, it's the usual suspects, but it's the thoughtful selection of those that seem to have the most applicability to multiple myeloma," Perkins says.

So far, only PIs have demonstrated single-agent activity in the disease, and Genmab's anti-CD38 has hinted at it; other pathways will likely exert their effect synergistically. "For instance, the HDAC [histone deacetylase] inhibitors by themselves don't really have great activity, but they are useful to overcome proteasome inhibitor resistance and potentially may enhance the efficacy of proteasome inhibitors," argues Lonial. "By the same token, antibodies to date have not been terribly successful in multiple myeloma, but the combination of lenalidomide with monoclonals looks quite exciting."

The challenge, he says, will be making sense of this diversity of treatment. Genomics is sure to play a part; a multiple myeloma tumor sequencing study published last year found that 4% of patients carried mutations that might respond to BRAF inhibitors like Roche/Genentech's Zelboraf (vemurafenib), and which have never been tested for the disease (*Nature*, **471**, 467–472, 2011). "Identifying which of the subsets of patients will gain greatest benefit after a majority of patients have already had a major response, I think, represents the next forefront of where we want to be."

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