Biotech comes to its 'antisenses' after hard-won drug approval

"With any brand new technology, you never know when the world will be ready for it." So said Paul Boni, an analyst at Punk, Ziegel & Knoll, in 1998 (as quoted by the *New York Times*), after the US Food and Drug Administration (FDA) approved its first gene-silencing 'antisense therapy', a drug known as Vitravene (fomivirsen), for the treatment of cytomegalovirus infections in individuals with weakened immune systems.

The arrival of Vitravene, a short strand of 21 DNA molecular units that blocks viral replication, was hailed as a major milestone for the biotech industry and was widely anticipated to usher in a new era of antisense products. But no more came. And by the middle of the last decade, Isis Pharmaceuticals, the Carlsbad, California–based company behind Vitravene, ended up pulling the therapy from the market because improvements in other antiretrovirals had effectively eliminated the drug's target market. Boni's cautionary words proved all too prescient.

Fifteen years after that first approval, however, antisense technology finally seems ready to make an impact. On 29 January, Isis won approval for another antisense drug—Kynamro (mipomersen), for the treatment of homozygous familial hypercholesterolemia (HoFH), a rare genetic disorder in which the body lack the ability to remove 'bad' cholesterol from the bloodstream. The drug is now being marketed by the French giant Sanofi, and several other antisense products are currently in late-stage clinical development.

"This is the end of the beginning for antisense," says Isis's chief executive Stanley Crooke. "We feel this is a critical step in the final validation of the technology."

First developed 35 years ago, the strategy of silencing genes by introducing short antisense stretches of DNA or other nucleic acids that are complementary to an mRNA target has proven useful in laboratory experiments, but translating the technology into the clinic has presented a challenge. For Kynamro, the key was a chemical alteration at both ends of the DNA strand. With this change, the product has an enhanced half-life, stronger affinity for its target RNA and a reduced proinflammatory side effect—all improvements in areas that have previously sunk antisense candidates in clinical testing.

This modification, Crooke says, "is the critical step that we took about 12 years ago, the product of thousands of tiny incremental steps." Isis currently has 26 candidate antisense drugs in its preclinical and clinical pipeline for treating a range of cardiovascular, metabolic and other types of disorders—the vast majority of which incorporate this chemistry, including an antisense drug that rescued hearing in a mouse model of human deafness, as reported in this month's issue of *Nature Medicine* (see page 345).

Right tissue, right time

Perhaps as important as chemistry was the molecular target Isis chose for Kynamro. Administered in weekly injections just below the skin, the drug tends to accumulate in the liver and other organs involved in blood filtration, although the uptake mechanisms remain unclear. This liver build-up led the European Medicines Agency to reject Isis's agent in December 2012, citing concerns over liver toxicity, but it could also help explain the success of Kynamro—a drug designed to block the synthesis of apolipoprotein B100, an important structural compound of low-density lipoprotein (LDL) synthesized in the liver. In a phase 3 trial involving 51 people with HoFH, Kynamro treatment led to a 25% average reduction in LDL cholesterol levels, compared to no significant change in participants on placebo (*Lancet* **375**, 998–1006, 2010).

Still, critics caution that the tendency of antisense products to build up in certain organs could prevent the technology from becoming a widespread drug platform. "The big problem is delivery, delivery, delivery," says Cy Stein, an oncologist at City of Hope in Los Angeles.

Stein, an early antisense pioneer, experienced this problem firsthand after he co-developed Genasense (oblimersen), an antisense molecule designed to silence B cell lymphoma 2 (BCL2), a protein implicated in a variety of cancers. Genta, the New Jersey–based company behind the drug, filed for FDA approval for Genasense for the treatment melanoma and chronic lymphocytic leukemia in 2003 and 2006, respectively, but the drug was rejected in both cases for lack of efficacy. Between a harsh tumor environment that proved inhospitable to drug entry and the tendency for antisense DNA to accumulate only in a few organs, "targeting cancer with these molecules is just not feasible," Stein says. Genta filed for bankruptcy last year.

One workaround is to apply antisense drugs directly where they're needed. Isis is taking this approach with its spinal muscular atrophy drug, which is injected into the fluid-filled space at the base of the spinal cord to target the motor neurons that are defective in the disease (see *Nat. Med.* **18**, 1602–1606, 2012). And Gene Signal, a company based in Lausanne, Switzerland, is advancing a topical antisense drug, administered in the form of eyedrops, designed to prevent corneal graft rejection and neovascular glaucoma.

With close to a dozen antisense products now in mid- to late-stage clinical development (see 'Making antisense of the drug pipeline'), many in the field are clearly buoyed. But Boni's warning continues to reverberate.

"While it is a nice validation that another antisense drug was approved by the FDA," says Chris Garabedian, chief executive of Cambridge, Massachusetts–based Sarepta Therapeutics, which is developing antisense compounds to treat Duchenne's muscular dystrophy (DMD), a rare genetic musculoskeletal disease, "we believe the success of eteplirsen, our lead DMD drug, will be based on its [own] efficacy and safety profile."

Kevin Jiang

Making antisense of the drug pipeline: Antisense therapies in mid- to late-stage clinical development.

Drug	Company	Disease	Phase
Kynamro (mipomersen)	Isis Pharmaceuticals and Sanofi	Homozygous familial hypercholesterolemia	Approved
Drisapersen	Prosensa and GlaxoSmithKline	Duchenne's muscular dystrophy	3
Custirsen	OncoGenex, Teva Pharmaceuticals and Isis	Prostate cancer and lung cancer	3
Aganirsen	Gene Signal	Progressive corneal neovascularization	3
Trabedersen	Antisense Pharma	Anaplastic astrocytoma and glioblastoma	3
Eteplirsen	Sarepta Therapeutics	Duchenne's muscular dystrophy	2
ATL1102	Antisense Therapeutics and Isis	Multiple sclerosis	2
ISIS-APOCIII$_{Rx}$	Isis	Hypertriglyceridemia	2
ISIS-CRP$_{Rx}$	Isis	Rheumatoid arthritis	2
ISIS-FXI$_{Rx}$	Isis	Clotting disorders	2
ISIS-EIF4E$_{Rx}$	Isis and Eli Lilly	Non–small-cell lung cancer and prostate cancer	2
EXC 001	Pfizer and Isis	Skin scarring	2
iCo-007	iCo Therapeutics and Isis	Macular edema	2
Alicaforsen	Atlantic Pharmaceuticals and Isis	Ulcerative colitis	2
OGX-427	Oncogenex and Isis	Bladder cancer and prostate cancer	2