Second RNAi drug approved

The European Medicines Agency has recommended approval for Alnylam's Givlaari (givosiran) for acute hepatic porphyria (AHP). This is the second RNA interference (RNAi) drug to secure approval in both the European Union and the United States, and the first treatment for AHP, a rare and life-threatening genetic condition in which patients lack the enzymes needed to produce heme.

Givlaari is an mRNA-targeting siRNA drug that lowers the expression of aminolevulinic acid synthase 1 (ALAS1), a liver enzyme that is involved in an early step in heme production. By downregulating ALAS1, the drug in turn lowers blood levels of aminolevulinic acid and porphobilinogen, neurotoxic intermediates that are associated with AHP symptoms including severe abdominal pain. In a six-month pivotal trial, patients treated with Givlaari experienced 70% fewer porphyria attacks than did placebo recipients. Common adverse reactions included nausea and injection site reactions.

The FDA approved the drug in November 2019. Analysts forecast annual global sales of $560 million for the siRNA candidate by 2025, according to data from the Cortellis database.

The only other approved RNAi drug is Alnylam's transthyretin-directed patisiran, approved in 2018 for hereditary transthyretin-mediated amyloidosis.

Alnylam, the RNAi pioneer, is also testing the utility of its emerging modality in other late-stage development programs. Its lumasiran, directed at hydroxyacid oxidase 1 mRNA, is under review in both the United States and European Union for primary hyperoxaluria type 1. The company is also running phase 3 trials of a next-generation transthyretin-directed candidate, vutrisiran, for transthyretin-mediated amyloidosis.

Another RNAi drug under regulatory review is the cholesterol-lowering agent inclisiran. The *PCSK9*-directed siRNA drug was developed by Alnylam, licensed to The Medicines Company and then acquired last year by Novartis. And Sanofi, under license from Alnylam, is testing the thrombin-directed fitusiran in pivotal trails in hemophilia.

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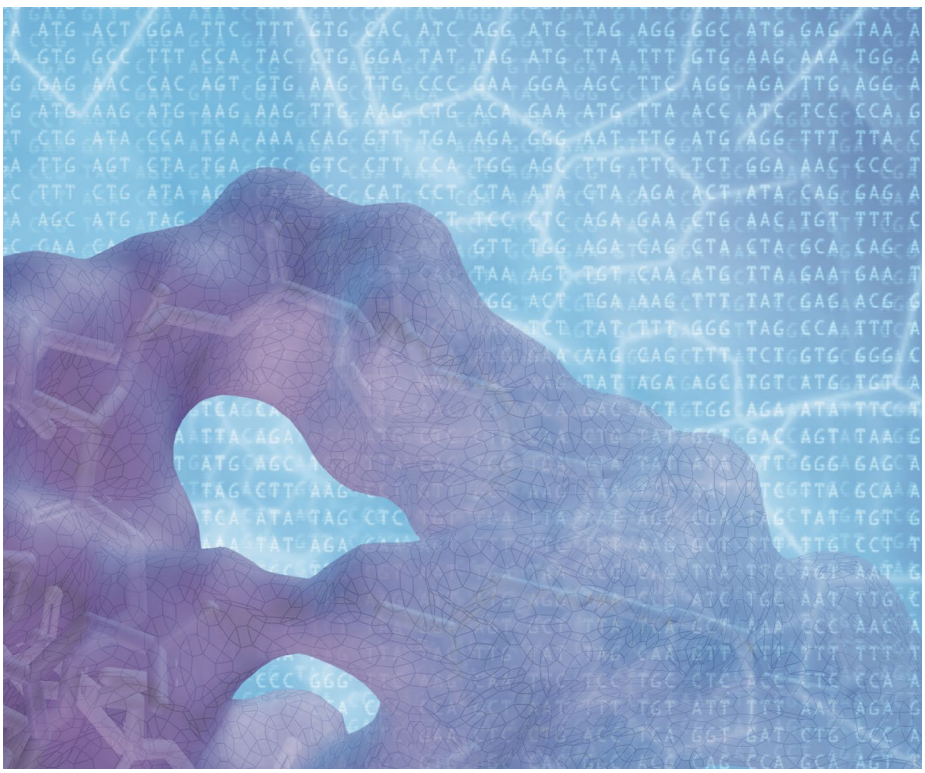
IGF-1R drugs travel from cancer cradle to Graves'

One of the most intensively investigated molecular targets in oncology proves its therapeutic worth for thyroid eye disease.

The first antibody drug targeting the insulin-like growth factor 1 receptor (IGF-1R) won regulatory approval in January — although not for the treatment of cancer, the indication first pursued more than a decade ago in some 30 different development programs involving experimental IGF-1R inhibitors. Instead, Horizon Therapeutics' Tepezza (teprotumumab) became the first and only medicine approved by the US Food and Drug Administration for the treatment of thyroid eye disease (TED), a vision-threatening autoimmune disorder, also known as Graves' orbitopathy, in which the fatty tissue and muscles around the eye become inflamed, pushing the eyeball outward.

Guido Magni, a former Roche executive who oversaw Tepezza's clinical development, credits the success of the drug to an outside-the-box kind of thinking that was in short supply years ago ten years ago when IGF-1R became one of the most intensively investigated molecular targets in the oncology. At the time, every company was focused on inhibiting the signaling cascade activated by IGF-1R in tumor cells. Nobody considered other disease settings — which is one of the "drawbacks of guys working in oncology only thinking about oncology," says Magni, who helped reposition the monoclonal antibody after leaving Roche and joining Versant Ventures in Basel, Switzerland, where he is now a partner. "We need more cross fertilization between therapeutic areas."

Yet just because IGF-1R inhibition found its first clinical niche in ophthalmology, not in oncology, "it doesn't mean that [IGF-1R] is not a valid target in all cancers," says Helen Chen, associate chief of the Investigational Drug Branch at the US National Cancer Institute. Indeed,



Insulin-like growth factor (IGF-1) has long been in biopharma industry's sights. Credit: Kenneth Eward / BioGrafx / Science Source