Sanofi's dengue vaccine first to complete phase 3

A verdict on the first-ever dengue vaccine candidate to reach phase 3 trials is expected by the end of the summer. In April, Sanofi Pasteur, of Lyon, France, announced that ChimeriVax-dengue, a recombinant DNA vaccine, achieved its primary clinical endpoint in a phase 3 study. Results from a second phase 3 trial will be ready by late September. If those data are similar to the first, "the vaccine is likely to be licensed without a problem," says Duane Gubler, professor of emerging infectious diseases at Duke-National University, Singapore's Graduate School of Medicine. Banking on approval, Sanofi has already started production, a move some have described as a "huge gamble" in light of the vaccine's disappointing results from earlier studies, says Mark Clark, a pharmaceuticals analyst at Deutsche Bank in London.

So far, Sanofi has spent more than €1 ($1.35) billion to develop ChimeriVax-Dengue. The French drug maker has also invested €300 ($405) million in a new, dedicated manufacturing facility in Neuville-sur-Saône near Lyon. Last July, production began at the new facility. Starting production early means that, should the vaccine be approved, it could be on the market as early as the end of 2015, ahead of competitors. Melanie Saville, chief medical and clinical officer, dengue vaccine, at Sanofi, says the aim is "to minimize the time between the potential registration of our candidate vaccine and the moment it is available to the healthcare community." Demand for the vaccine could reach 2.4 to 3.5 billion doses over the first 5 years (*Hum. Vaccin.* **6**, 745–753, 2010).

Dengue, for which there are no approved vaccines or antivirals, is the world's fastest-growing tropical disease. Dengue is caused by one of four related, but distinct, flavivirus serotypes (DEN 1-4), spread by the bite of an infected *Aedes aegypti* mosquito. The boom in global travel and trade, urbanization, climate change and poor mosquito control have colluded to fuel dengue's dramatic increase. A 2013 study (*Nature* **496**, 504–507, 2013) estimated the current annual global incidence of dengue infection at about 390 million—a much higher figure than the World Health Organization estimate of 50 to 100 million.

Dengue is not only painful; it can be deadly. Symptoms may be absent or severe, and include high fever and excruciating joint pain; but individuals who have been infected with dengue once are more likely to have severe symptoms upon a second infection, including hemorrhagic disease—fatalities can exceed 20%. After infection by two different serotypes, however, subsequent infections usually cause only mild symptoms, if any.

Dengue vaccines have been under development since the 1940s. There are now six vaccine candidates (**Table 1**), with Sanofi's ChimeriVax the most advanced. Sanofi's candidate is a tetravalent vaccine composed of four recombinant, live, attenuated viruses (*Vaccine* **29**, 7229–7241, 2011). Each uses the 17D yellow fever virus as a replicative backbone to carry genes encoding structural proteins from one of the four dengue virus serotypes. This chimeric dengue vaccine (CYD) was initially developed by Acambis, which was acquired by Sanofi Pasteur in 2008.

Initial results showed ChimeriVax was safe but poorly effective. Phase 2b studies conducted in 4,000 Thai schoolchildren showed only 30.2% efficacy. The vaccine failed to protect against DEN-2—the most prevalent strain during the

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A bite from an infected *Aedes aegypti* mosquito can transmit dengue, known as 'bone breaking disease'.

Celgene shells out for antisense drug

Celgene has brought in a high-priced experimental drug it thinks has blockbuster potential. In April, the Summit, New Jersey–based big biotech paid dearly to get Nogra's GED-0301 for treating Crohn's disease and other gastrointestinal disorders. The price for GED-0301, a late-stage antisense drug, includes $710 million upfront—more than the combined upfront payments for all the technologies and product candidates licensed in its mainstay cancer franchise, where the vast bulk of its investments have been to date. The move, for a drug probably still five years from the clinic, shows the big biotech's confidence in this antisense technology, but seeking tax refuge outside of US may also have played into the high price of the deal with Dublin-based Nogra. GED-0301 is a first-generation synthetic single-stranded *O,O*-linked phosphorothioate oligonucleotide that binds the region 107–128 of the human Smad7 complementary DNA sequence. It contains two CpG motifs that have been chemically modified to avoid immunostimulatory effects. High levels of Smad7 amplify inflammatory signals in the gut of patients with Crohn's disease by blocking the immunosuppressive activity of transforming growth factor-1. Nogra completed a 166-patient phase 2 trial of the molecule in active Crohn's. GED-0301 has shown a "consistently high response rate and rate of remission after just four weeks of treatment," according to Scott Smith, president of inflammation and immunology. "I think you see here the coupling of the antisense technology with [a] delivery system that delivers the drug right on site in the gut," he said on a call discussing the deal with analysts. GED-0301 adds to Celgene's immunology franchise, which recently launched Otezla (apremilast), the first phosphodiesterase-4 inhibitor approved for treating a psoriatic condition (*Nat. Biotechnol.* **32**, 505, 2014).

Jacqualyn Fouse, Celgene CFO when the deal was struck (she was subsequently promoted to president of hematology and oncology), called the bidding process for GED-0301 "highly competitive." Some reckon the bidding war was sparked partly by Ireland's attractive corporate rate (roughly one-third of the US rate). That would attract buyers wishing to relocate their businesses there for tax reasons. Nogra itself changed its name from Giuliani International, a part of the Giuliani group, a specialty pharmaceutical operation in Italy focused on gastroenterology and dermatology, and set up an Irish identity in 2012.

Seeking tax refuge outside the US was part of the rationale for New York–based Pfizer's recent (and unsuccessful) bid for London's AstraZeneca. The strategy played out several times in pharma in 2013: for over-the-counter and generic drug maker Perrigo, which moved from Allegan, Michigan, to Dublin after the acquisition of Dublin's Elan, and for Actavis, a specialty pharma located in Parsippany, New Jersey, before buying another Dublin company, Warner Chilcotte.

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