Celgene eyes 'inverse vaccines' in Anokion and Delinia deals

Celgene is taking a twin-track approach to inducing tolerance as therapy for autoimmune disease through two deals it entered in January. Its acquisition of Cambridge, Massachusetts–based Delinia, for $300 million plus up to $475 million in milestones, brings it an engineered interleukin-2 (IL-2) drug that could have broad application in multiple autoimmune diseases. A research collaboration with Ecublens, Switzerland–based Anokion gives it access to two novel technologies, both of which tolerize the immune system in an antigen-specific fashion by exploiting the tolerance-induction processes that accompany apoptosis. That deal, which is worth $45 million upfront plus another $10 million in preclinical development milestones, includes an option for Celgene to purchase Anokion in the future. Officials at Summit, New Jersey–based Celgene declined to comment on whether it plans to develop a unified strategy in this area. These antigen-independent and antigen-specific approaches could be complementary, but each would need to be developed as a monotherapy before considering combinations. Even so, Celgene's moves are evidence that immune tolerance remains an area of active interest for big biotech and large pharma firms, notwithstanding its disappointing track record to date.

The two deals are all the more noteworthy as they come after several disappointments in the field. "All these efforts are almost invariably directed to the deletion of the relevant T-cell populations," says Pere Santamaria, a professor in the department of microbiology, immunology and infectious diseases at the University of Calgary, in Alberta, Canada. They rely, he adds, "on knowledge, which, at the moment, is fragmented and superficial, in my opinion."

Although the jury is out on some efforts—Merck, of Darmstadt, Germany, last year terminated its involvement in Apitope's multiple sclerosis (MS) therapy ATX-MS-1467 in advance of phase 2 data—others that have reached the clinic have stalled due to lack of interest from prospective partners or investors or have yet to deliver compelling efficacy data. Several newer approaches are still in preclinical development (**Table 1**).

But academic scientists and biotech startups have kept faith with the concept, given its potential to offer safer therapies than those currently available for a whole range of autoimmune diseases, such as type 1 diabetes, rheumatoid arthritis and MS. These conditions are usually defined as an aberrant autoimmune response against the body's own tissue, but that reaction is merely the downstream consequence of a loss of tolerance toward one or more self-antigens. "There are many ways to lose tolerance," says Jeffrey Hubbell, Anokion's scientific founder and CSO. "What initiates the disease in the beginning is still unknown." Possible mechanisms for re-establishing lost tolerance include the ordered deletion of autoreactive T cells and B cells, inducing anergy (or, T-cell exhaustion), triggering a switch from an effector to a regulatory phenotype, or stimulating the activation of regulatory T cells. An underlying aim is to achieve these effects through what is known as bystander regulation, by forming a tolerogenic milieu within the tissue or organ that is under attack. This goes beyond inducing tolerance to a single epitope or antigen—yet it does not require knowledge of every disease-associated autoantigen.

Courtesy of Innovation Forum Lausanne

Anokion's Kristen M. Lorentz and Stephan Kontos, part of the company's co-founding team.

Most existing biologic therapies for autoimmune disease—type 1 diabetes excepted—target the downstream autoimmune component of the problem. Cytokine antagonists, B-cell depletion agents, such as Rituxan (rituximab), T-cell costimulation inhibitors, such as Orencia (abatacept), and inhibitors of T-cell trafficking, such as Tysabri (natalizumab), have all been widely adopted. None is ideal. Not all patients respond to therapy, and many of those that do eventually become refractory. All of the approaches, moreover, are blunt instruments. They involve a generalized immunosuppression that leaves patients vulnerable to opportunistic infections. "Now it's time to get a little more elegant about it," says Saurabh Saha, Delinia's CEO and a venture partner at Cambridge, Massachusetts–based Atlas Venture, one of its investors.

Delinia's strategy builds on previous clinical experience with IL-2, a cytokine that has

Trump's pick rallies biosimilar makers

For the first time in 20 years, a physician has become US Secretary of Health and Human Services. On February 10, the Senate voted 52–47 to confirm Tom Price in the post under President Donald Trump. Price is an orthopedic surgeon and Republican congressman from Georgia, who has held a House seat since 2005. He staunchly opposed the Patient Protection and Affordable Care Act and remained a vocal critic of the policy. In his new capacity, Price is expected to lead efforts to dismantle it. Price's appointment was welcomed by the Biosimilars Forum—an industry group that includes Amgen, Boehringer Ingelheim, Merck, Pfizer, Samsung Bioepis, Sandoz and Teva. The group is set to lobby Price to increase access to biosimilars by reversing the current Centers for Medicare & Medicaid Services' reimbursement policy. Previously, in January, the agency finalized guidance to help biosimilar producers understand what data are necessary to demonstrate interchangeability with an originator product. The agency also reiterated naming recommendations first proposed in August 2015, designed to differentiate among non-interchangeable reference products.

Biogen pays Forward in Tecfidera dispute

Biogen has agreed to pay $1.25 billion to Danish biotech company Forward Pharma to settle part of a patent dispute over the Cambridge, Massachusetts–based drugmaker's top-selling multiple sclerosis drug Tecfidera (dimethyl fumarate). The deal will give Biogen co-exclusive licensing rights in the US and exclusive worldwide rights to the intellectual property related to the active ingredient, dimethyl fumarate. It does not, however, resolve existing patent litigation between the two companies regarding the use of dimethyl fumarate to treat multiple sclerosis (MS). Forward Pharma, which is using dimethyl fumarate to develop its own drug, challenged a Biogen patent on the ingredient, claiming it owns an earlier patent. Forward has filed an interference proceeding—which arises when two or more pending patents contain claims covering the same invention—with the US Patent and Trademark Office and a separate opposition proceeding with the European Patent Office. If Forward's patent claims prevail, it could receive annual royalties of up to 20% on Biogen's sales of Tecfidera. The MS drug generated $3.6 billion for Biogen in 2015. Biogen CEO Michel Vounatsos, eager to end the long-running litigation involving Tecfidera and move the company forward, said in a statement that the deal with Forward "will clarify and strengthen our intellectual property for Tecfidera." In December Biogen and its partner Ionis Pharmaceuticals won US Food and Drug Administration approval for the first spinal muscular atrophy treatment (*Nat. Biotechnol.* **35**, 99–100, 2017).