IN brief

Monsanto buys Climate Corporation for \$1.1 billion

St. Louis-based Monsanto in October announced plans to acquire the Climate Corp. of San Francisco, a company that describes itself as using “machine learning to predict the weather and other essential elements for agribusiness.” It provides farmers with specialized weather forecasting as well as a variety of insurance products to protect them against weather damage or other risks. This nearly \$1-billion cash purchase is expected to benefit farmers by supplying them with information about the many factors that affect the success of their crops, according to Monsanto. “Monsanto and other companies face a problem with the need for farmers to purchase seed well before they will know whether the expensive engineered traits will be needed,” says Doug Gurian-Sherman of the Union of Concerned Scientists in Washington, DC. “If Monsanto wants to convince farmers to pay more, maybe a lot more, for seed with engineered drought tolerance, it would be very helpful to be able to have some prediction of the likelihood of drought at the time of seed purchase. In the future, other climate or weather-related traits may also face the same dilemma.” Charles Benbrook of Washington State University in Pullman, who closely follows developments involving agbiotech, says, “Next-generation increase[s] in profits are in the tech fees, [which] are going to be driven by the perceived value of the technology package, and will go well beyond crop genetics plus GE [genetically engineered] traits.” The trend is to bundle products, he adds, and “Monsanto is hoping that adding detailed climate data to the mix, no doubt via electronic delivery to a farmer’s GPS and precision ag machinery and record-keeping systems, will be one more reason to stick with the big M.”

Jeffrey L. Fox

IN their words

“Always always always underpromise and overdeliver.” Bonnie Fendrock, former CEO at Medford, Massachusetts-based Hepregen talks about setbacks and failures, stressing the importance of finessing

and managing board expectations. (*Boston Business Journal*, 25 October 2013)

“The challenge to the people of the states was to put a man on the moon in a decade. It’s taken 30 years to get [a malaria] vaccine from the idea to where we are today. So in a strange way, developing a vaccine for malaria makes putting a man on the moon look relatively straightforward.” Sir Andrew Witty, CEO of GlaxoSmithKline in a conversation with Steve Forbes, editor in chief *Forbes*. (*Forbes*, 29 October 2013)

First-in-class guanylate cyclase stimulator approved for PAH

In October, the US Food and Drug Administration gave the green light to Bayer’s of Leverkusen, Germany, Adempas (riociguat) for the treatment of pulmonary arterial hypertension (PAH) as well as chronic thromboembolic pulmonary hypertension—the only nonsurgical therapy for the latter. PAH is a progressive, often lethal, disease characterized by increased resistance in the pulmonary vasculature, ultimately leading to heart failure, vascular remodeling and localized thrombosis. Adempas is the first approved agent to specifically target soluble guanylate cyclase (sGC), a key component in the nitric oxide signaling pathway.

PAH involves the tightening of lung blood vessels in the lung.

sGC is activated by nitric oxide and catalyzes the synthesis of cyclic guanosine monophosphate (cGMP), which induces vasodilation and inhibits proliferation of vascular smooth muscle cells, fibrosis and platelet aggregation. In PAH patients, the nitric oxide-sGC-cGMP pathway signaling is disrupted at many levels, and reduced levels of nitric oxide are a common feature of the disorder.

Among approved treatment options are phosphodiesterase type 5 (PDE5) inhibitors, such as New York-based Pfizer’s Revatio (sildenafil, also marketed as Viagra) and Indianapolis-based Lilly’s Adcirca (tadalafil), which prevent the degradation of cGMP. However, approximately half of patients fail to respond to these drugs, says Oleg Evgenov, of Massachusetts General Hospital in Boston, due to low nitric oxide levels or impaired sensitivity of sGC by nitric oxide, leading to less cGMP production. Moreover, when PDE-5 is inhibited, other PDEs may compensate for it.

Rather than preventing cGMP degradation, sGC stimulators increase cGMP production, and their downstream effects are unaffected by low nitric oxide levels. “sGC stimulators could be good drugs for nonresponders to PDE5 inhibitors,” says Mark Gladwin of the University of Pittsburgh in Pennsylvania, who believes that the latter will continue to remain an important treatment option, especially with the introduction of generic sildenafil for PAH, which were launched by several companies in the last year.

Although sGC stimulators should not be combined with PDE5 inhibitors because this can lead to systemic hypotension, the phase 3 trial of Adempas demonstrated a benefit when combined with another PAH drug class, the endothelin receptor antagonists, which also relax the pulmonary arteries. “For the first time, we had a drug that showed an improvement for patients already on background therapy,” says Hossein-Ardeschir Ghofrani of the University of Giessen in Germany, lead investigator in Adempas’s phase 3 trial in PAH. “It was a very encouraging study, but we still need to see the long-term benefits of the therapy in PAH patients, including reduced mortality,” says Evgenov.

In October, Opsumit (macitentan), Actelion’s successor to its blockbuster endothelin receptor antagonist Tracleer (bosentan) was also approved by the FDA for PAH. Opsumit also an endothelin receptor antagonist, showed an improved safety profile compared with Tracleer, which has liver toxicity. Opsumit also was the first PAH drug tested with morbidity and mortality as primary endpoints.

Besides sGC stimulators and PDE5 inhibitors, another way to target the nitric oxide-sGC-CMP pathway is through inhaled delivery of nitric oxide to the lungs, which, if approved, would most likely be used in patients already taking oral therapies. Ikaria of Hampton, New Jersey, which markets inhaled nitric oxide as INOMAX to treat newborns suffering from hypoxic respiratory failure, is currently testing inhaled nitric oxide on top of other PAH therapies in a phase 2 trial, as well as a proprietary pulse delivery system for ambulatory use.

Malini Guha Freehold, New Jersey