irrefutable,” he says. “Is it driving the disease? That’s the big question.”

Titration of the cGAS–STING pathway either down or up is likely to have effects on many aspects of immune signaling. “It’s not just interferon signaling—that’s clear,” says Crow. Other cytokines may also be involved. “The big issue, of course, is that not all lupus patients are the same,” van Elsas says. It is not clear at this point whether the trial failed because of patient heterogeneity or because of the target. The result did not diminish Lilly’s enthusiasm for the Aduro deal, he says. But it will further complicate the interrogation of the cGAS–STING pathway as a mediator of autoimmune disease.

Nimbus Therapeutics identified its small-molecule STING antagonists through its computational chemistry approach to drug discovery. This relies heavily on its privileged access to the molecular simulation capabilities of its cofounder, the Bill Gates-backed *in silico* drug discovery and materials science firm Schrödinger. The Nimbus program, part of a collaboration

with Celgene forged in 2017, will now be inherited by Bristol-Myers Squibb following the big pharma’s acquisition of Celgene in early January.

Inhibiting an immune signaling pathway, according to conventional thinking, should be easier to accomplish than stimulating one. From a drug development standpoint it’s easier to discover a compound that blocks an activity than one that potentiates activity. What’s more, the safety margin is generally wider; with a drug mechanism involving immune activation, inhibitors should have fewer concerns related to the triggering of a devastating release of cytokines.

The two most compelling targets in the cGAS–STING pathway are cGAS synthase and STING, says Gary Glick, CEO of IFM Therapeutics, a holding company whose two subsidiaries are taking forward cGAS–STING antagonist and inflammasome antagonist programs, following Bristol-Myers Squibb’s acquisition in 2017 of the original IFM for its STING agonist assets. “I can envision other points of intersection,

but those are the ones which make most sense and which are receiving most attention,” he says. Drugging cGAS synthase has proven difficult, however. “A lot of pharmas have tried, and most have failed,” he says. IFM is working on this target but is more advanced with STING. As it is already tractable to agonists, it should also be possible to antagonize the protein, he says.

Firms focused on inhibiting cGAS–STING have yet to declare which indications they will focus on initially. “The likelihood is we would take a two-pronged approach,” says Glick. That would entail trials in rare conditions with a tight genetic linkage to interferon overproduction, as well as more common chronic conditions in which cGAS–STING signaling is also implicated. □

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Around the world in a month

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