are so far indistinguishable. Blocking the cytokine is more specific, sparing the other five IL-17 family members (B–F), and thus is theoretically safer. But targeting the receptor could be more efficacious, notes Bing Yao, senior vice president of the respiratory, inflammatory and autoimmune disease unit at MedImmune in Gaithersburg, Maryland, the biologics arm of AstraZeneca. That's because both IL-17A and IL-17F are present in psoriasis biopsies, and both signal through the IL-17RA receptor, which Amgen's molecule blocks.

A third approach also shows great promise. Merck in Whitehouse Station, New Jersey, Janssen Biotech in Horsham, Pennsylvania (a division of Johnson & Johnson (J&J) in New Brunswick, New Jersey), and Amgen all have antibodies in clinical development targeting the p19 subunit of IL-23 (**Table 1**). IL-23 is the main differentiation and survival cytokine for T_H17 cells and also stimulates other lymphocyte responses. It has two subunits: p19 and p40. J&J's Stelara (ustekinumab), approved for psoriasis in 2009, targets the p40 subunit, and its efficacy strongly validates IL-23 as a target (*Nat. Biotechnol.* **29**, 563–566, 2011). But because p40 is shared with another cytokine, IL-12 (crucial for T_H1 cell differentiation), anti-IL-23 mAbs also block IL-12 signaling. Targeting p19 would provide more specific IL-23 inhibition, and thus be theoretically safer than Stelara. (Dermatologists use Stelara cautiously because of concerns about cardiovascular side effects, which were associated with another investigational anti-p40 antibody, briakinumab, from Abbott Laboratories in Abbott Park, Illinois.)

Companies want to avoid hitting IL-12 not only to limit side effects and preserve T_H1 immunity but also because the presence of T_H1 cytokines may actually help inhibit T_H17 cells, says Krueger. In a phase 1 trial reported last December, all five psoriasis patients receiving a single subcutaneous 300-mg dose of J&J's anti-p19 antibody achieved a PASI 100—full clearance.

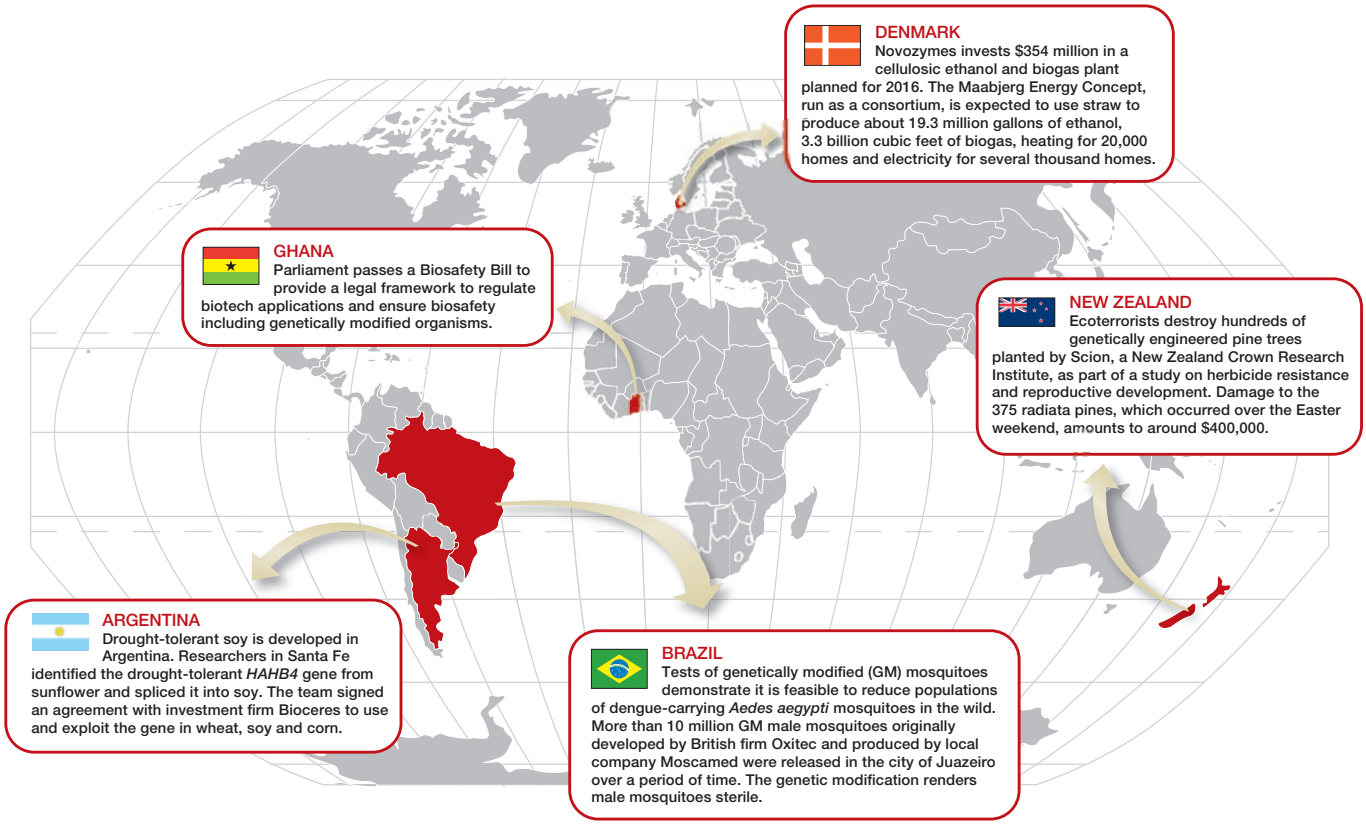
Results like this in psoriasis haven't been matched in rheumatoid arthritis. In data reported at the American College of Rheumatology annual meeting last November, Lilly's ixekizumab, in phase 2, produced about a 40% ACR20 response (20% reduction in symptom scores) in patients who had failed anti-TNF-α therapy, compared with a 23% ACR20 for placebo—a relatively modest difference. "There is a place, potentially, for this drug in patients who don't respond to other pathways," says Lilly's Banerjee. "It's still effective." But Lilly does not yet have definite plans for phase 3.

Banerjee speculated that IL-17 may be less critical in rheumatoid arthritis than in psoriasis. "In a heterogeneous disease like RA [rheumatoid arthritis], it appears that TNF-α may be playing a more important role," he says. As for other autoimmune indications, Amgen suspended its brodalumab phase 2 Crohn's disease trials owing to cases of worsening disease in the treated group. "Perhaps psoriasis is just a lucky case that the role of IL-17 in the disease is more singular than it is in diseases like RA, which is actually much more complex," says Krueger.

Psoriasis should be reward enough. "Everybody needs a new growth driver," says Tony Butler, an analyst at Barclays Capital in New York. "And if you have fewer side effects…you have multibillion dollar potential just in psoriasis alone."

Ken Garber *Ann Arbor, Michigan*

Around the world in a month



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