chemokines can still bind the CXCR1 and CXCR2 receptors to propagate an immune-suppressive microenvironment. These include granulocyte chemotactic protein 2 as a ligand for CXCR1, and growth neutrophil-activating proteins 2 and 3 as ligands for CXCR2. "There's a bit of a head-scratcher about whether [blocking] IL-8 will give the desired results since CXCR2 is still open and ready for business with the small handful of other ligands that will engage it with high affinity," Schall says. ChemoCentryx is currently developing a small-molecule inhibitor of CXCR2 that the company plans to take into the clinic next year.

AstraZeneca, meanwhile, has already begun human testing of a CXCR2 inhibitor called AZD5069. The drug is currently in dose-escalating phase 1/2 trials in combination with an experimental checkpoint inhibitor—the anti-programmed-cell-death ligand-1 drug durvalumab—for metastatic pancreatic cancer patients, as well as for people with head and neck squamous cell carcinomas. In June, a team that included Simon Barry, a senior principal scientist with AstraZeneca's oncology research division in Macclesfield, Cheshire, UK, and collaborators Owen Sansom and Jennifer Morton, from the Cancer Research UK Beatson Institute in Glasgow, described how blocking CXCR2 prevented MDSCs from trafficking to the tumor bed. This in turn enhanced T-cell entry and conferred sensitivity to a programmed-cell-death-1-targeted antibody in a mouse model of pancreatic ductal adenocarcinoma (*Cancer Cell* **29**, 832–845, 2016).

Waugh is also planning to deliver AZD5069 as an add-on to other kinds of cancer therapies. With funding from Prostate Cancer UK and AstraZeneca, he and his collaborators—Andrea Alimonti of the Institute of Oncology Research in Bellinzona, Switzerland, and Johann de Bono of the Institute of Cancer Research in London—expect to launch a trial next year combining AZD5069 with the androgen receptor inhibitor Xtandi (enzalutamide)—in men with castration-resistant prostate cancer who don't respond to Xtandi therapy alone.

"Interfering with these myeloid lineages has a dramatic effect on the subsequent response to an additional therapy," says Barry. "Both immunotherapy and tumor-cell-targeted therapies such as chemotherapy or even androgen treatment could be enhanced by inhibiting the function of CXCR2-dependent cell types."

But dialing down IL-8 signaling could have adverse consequences on a person's ability to fight disease given the chemokine's role directing neutrophils to sites of inflammation and infection. That's another good reason, asserts Schall, for targeting CXCR2, the receptor most active in tumors, while leaving IL-8 to engage with CXCR1 elsewhere in the body. But in early trials to date in patients with inflammatory conditions, no major toxicity issues have arisen from agents directed at the IL-8 pathway, including with Abgenix's ABX-IL8 antibody, or with BMS's HuMax-IL8, which was tested over a decade ago in 31 patients with a skin condition called palmoplantar pustulosis.

"There is very little clinical data available at present that raises a safety profile concern from targeting of IL-8 signaling in respiratory, arthritic or oncology conditions," Waugh says. "Antibodies or small-molecule strategies seem to be well-tolerated."

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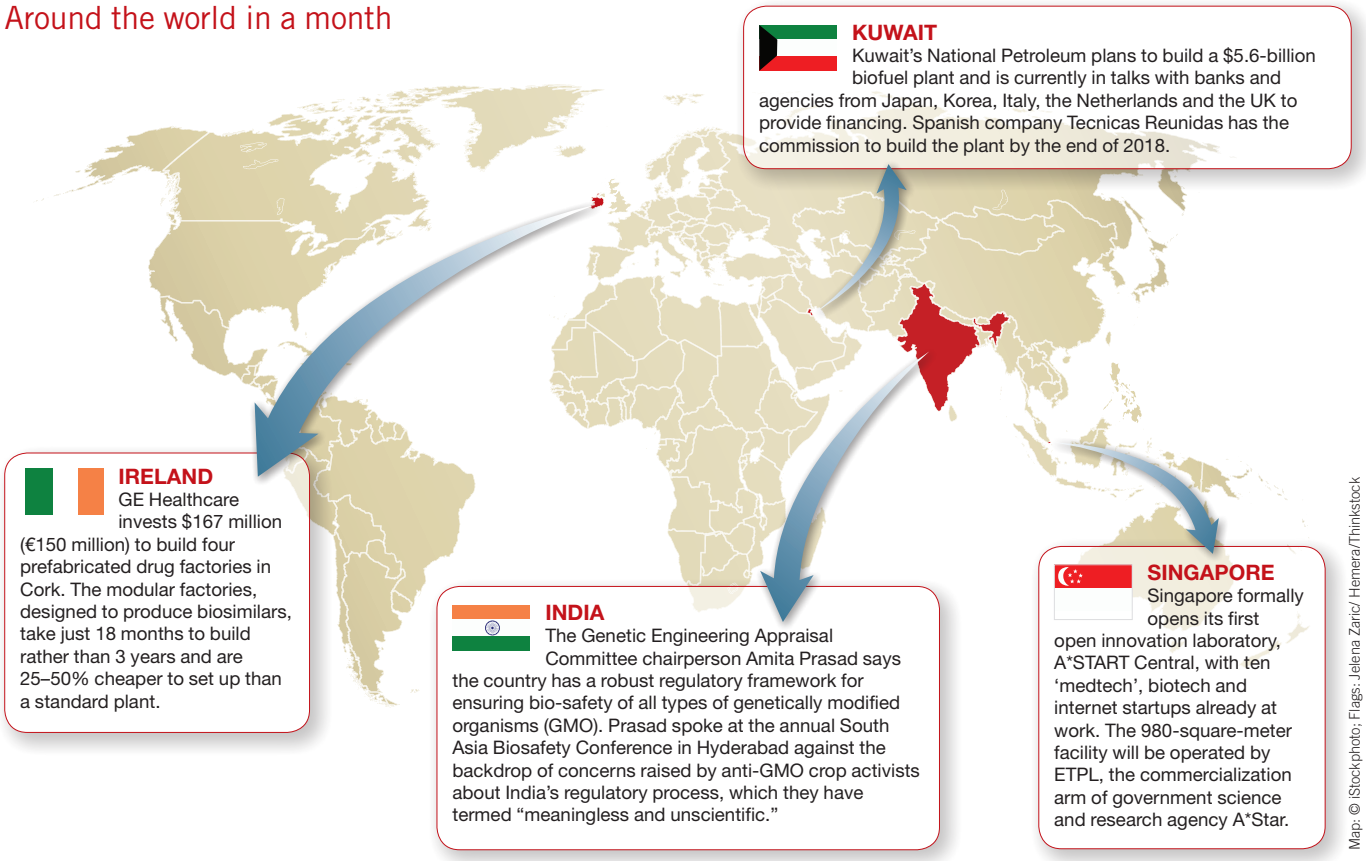
Around the world in a month



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