undergoing further processing to become functional molecules. DsiRNAs are slightly longer and bind to and are cleaved by Dicer, a step, its developers claim, that increases the efficiency of RISC assembly and the subsequent RNAi effect. "We have been able to optimize neural delivery by alteration of the chemical characteristics of the loop end of our molecule," says Fambrough. "We have a free hand to change the chemistry in the loop end in any way we want, without impairing the RNAi function of the molecule."

Alnylam has developed a further general refinement to its ligand-conjugated siRNA technology, which could widen the therapeutic window for its siRNA molecules. The technology, part of its 'Enhanced Stabilization Chemistry+' (ESC+) platform, involves the inclusion of a glycol nucleic acid base at a specific location in the seed region (bases 2–8 from the 5′ end) of siRNAs, which reduces off-target effects that can arise at high doses, without affecting potency. "We're learning how to make sure the molecule hits exactly where we want it to hit and nowhere else," Fitzgerald says. "The ESC+ chemistry is maybe not that important for applications in the liver, where the doses needed to achieve therapeutic effects are pretty low," says Han, who is a postdoctoral researcher in Rossi's lab. "However, if they find themselves needing to apply higher doses to get therapeutic effects in tissues outside of the liver, the ESC+ chemistry may give them an extra safety margin," he says.

Of course, certain questions about the potential utility of a given drug candidate can only be answered in a clinical trial. "No matter how good the data look in animal models, there is always some uncertainty regarding potency, biodistribution and safety in moving to humans for a new tissue type with a new ligand–siRNA combination," says Han. The upcoming clinical trials will not all be positive, but they help to further the evolution of what is currently a niche therapeutic modality into a more generally applicable technology. ❐

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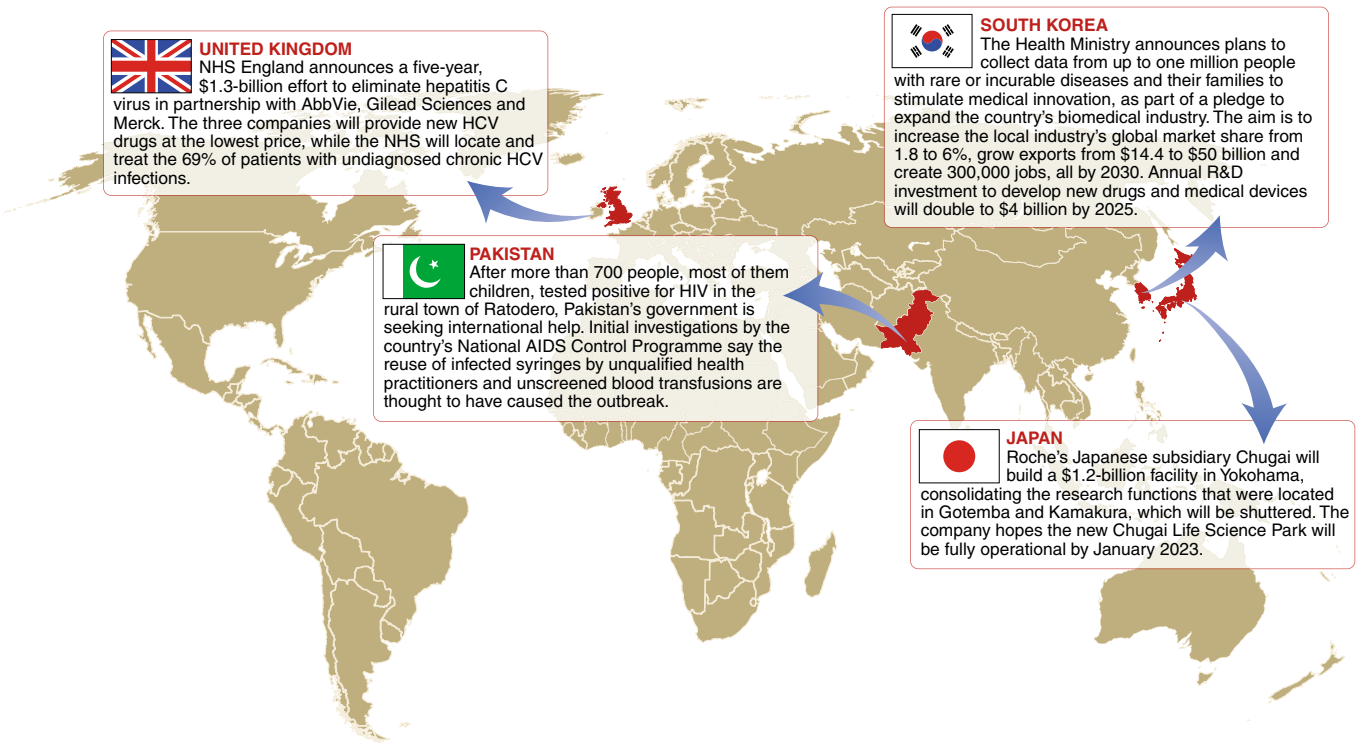
Around the world in a month



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